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PERFORMANCE OF THE STATIONARY VERTICAL-SCREEN OXYGENATOR (MAYO-GIBBON)

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SOME GENERAL information on the transfer of oxygen in the stationary vertical-screen oxygenator (Mayo-Gibbon) with blood flowing at rates of 160 to 260 ml. per minute per screen has been published.[1] The present study confirms the previous impression that the performance of this apparatus is reproducible and indicates further that oxygen transfer is related to the amount of reduced hemoglobin entering the oxygenator.

METHODS

Oxygen tension in blood was measured by a polarographic method using the Clark oxygen electrode.[2] The electrodes were calibrated at the temperature observed at the electrode during the perfusion. Three calibration points were obtained, and a calibration line for each electrode was constructed.

The oxygen content, oxygen capacity, and carbon dioxide content of the blood were determined according to the method of Van Slyke and Neill.[3] The amount of hemoglobin was calculated by dividing the corrected oxygen

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capacity[4] by 1.34. The amount of dissolved oxygen was calculated in Cases 1 through 10 from the oxygen tension observed at the appropriate oxygen electrode and the solubility coefficient for whole blood (0.023 ml. [STPD] of oxygen per milliliter of solution at an oxygen pressure [pO_2] of 760 mm. Hg at 37° C.).[4] In Cases 11 through 17, the amount of dissolved oxygen was assumed to be 0.1 and 0.3 volume per cent, respectively, in samples obtained from blood entering and leaving the oxygenator. The amount of oxyhemoglobin was calculated by subtracting the amount of dissolved oxygen from the total oxygen content and dividing the remainder by 1.34. The percentage saturation of hemoglobin with oxygen was calculated as 100 × (concentration of oxyhemoglobin ÷ concentration of total hemoglobin). The amount of reduced hemoglobin was obtained by subtracting the oxyhemoglobin content

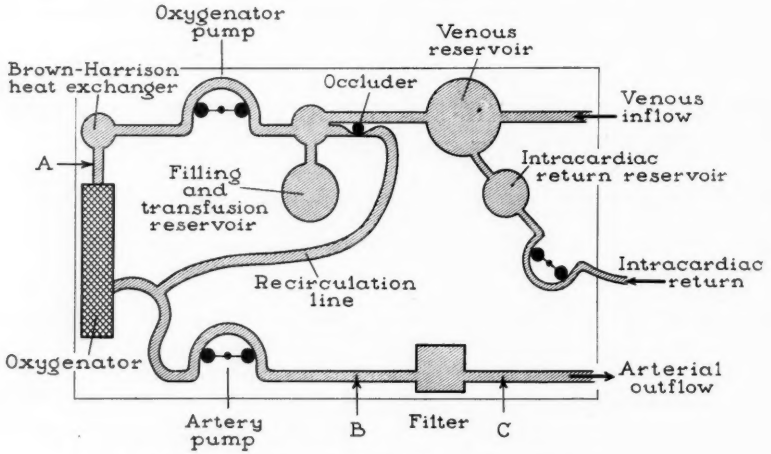

Fig. 1.—Flow circuit of Mayo-Gibbon pump oxygenator.

from the total hemoglobin content. The amount of oxygen added per screen was calculated from the difference in oxygen content of blood entering and leaving the oxygenator and from the screen flow; it included both chemically combined and dissolved oxygen. The pH was determined at 37° C. in a Cambridge Research Model pH meter. The carbon dioxide pressure (pCO_2) was estimated from the Singer-Hastings nomogram.[5] Methods used for the in vitro study were different only in that the percentage saturation of hemoglobin was determined with a Wood cuvette oximeter,[6] and the calculated rates of oxygen transfer did not include any oxygen in physical solution.

The surface area in square meters for patients weighing more than 15.5 kilograms was obtained from a height-weight nomogram based on the DuBois formula. The surface area of patients weighing 15.5 kilograms or less was obtained from a table based on weight.[7] Basal consumption of oxygen in the first group was calculated from values based on age, sex, and surface area[8]; in the second group, it was determined from values based on sex and weight.[9]

PROCEDURE

The performance of the oxygenator was studied during the normothermic perfusion of 17 patients and during one in vitro study. During total cardiopulmonary bypass, the recirculation line was closed (see Fig. 1 for the flow circuit). Blood passed from the venous reservoir through the oxygenator once and then into the arterial system of the patient. The oxygenator was ventilated with 98 per cent oxygen and 2 per cent carbon dioxide at a flow rate of 10 L. per minute. The design of the individual screen (30 cm. wide, 60 cm. high) has been published.[1] Screen flows were established prior to the

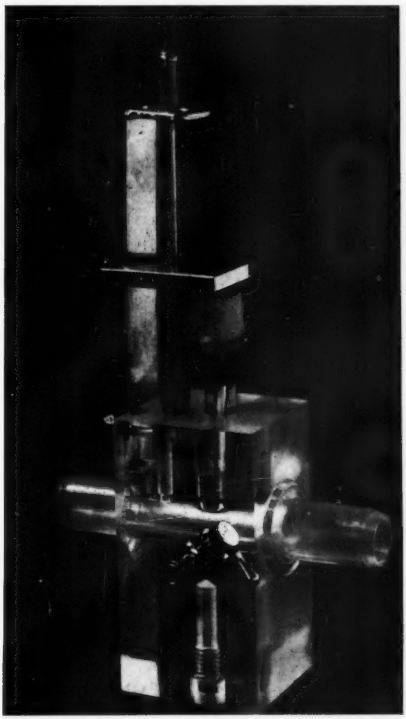

Fig. 2.—Manifold with thermistor probe, oxygen electrode, and sample cock.

institution of perfusion and remained unchanged throughout each individual perfusion. Anesthesia was accomplished by the use of thiopental sodium, nitrous oxide, and succinylcholine.

Fig. 2 illustrates the manifold that provided for the placement of an oxygen electrode, a thermistor and a sample cock in the lines entering the oxygenator (*A* in Fig. 1) and leaving it (*B* in Fig. 1). In a preliminary study, the oxygen tensions observed at site *B* were not different from those observed at a second site distal to the arterial filter (*C* in Fig. 1). In Cases 1 through 10, oxygen tensions were determined at sites *A* and *B* at 1-minute

TABLE I. DATA DURING 17 CLINICAL PERFUSIONS WITH THE VERTICAL-SCREEN OXYGENATOR

CASE	SURFACE AREA (SQ. METERS)	BASAL OXYGEN UPTAKE (PREDICTED) (ML./MIN./SQ. METER)	PERFUSION FACTORS			BLOOD ENTERING OXYGENATOR*			BLOOD LEAVING OXYGENATOR					OXYGEN ADDED (ML/MIN./SCREEN)
			SCREENS (NUMBER)	SCREEN FLOW (ML./MIN.)	HEMOGLOBIN (GM./100 ML.)	pO_2† (MM. Hg)	OXYGEN CONTENT (VOL. %)	HEMOGLOBIN SATURATION (%)	pO_2† (MM. Hg)	OXYGEN CONTENT (VOL. %)	HEMOGLOBIN SATURATION (%)	pH	pCO_2 (MM. Hg)	
1	1.48	—	13	228	—	37	—	—	110	—	—	—	—	—
2	0.60	—	7	209	—	60	—	—	205	—	—	—	—	—
3	1.15	—	13	212	—	50	—	—	280	—	—	—	—	—
4	0.80	—	9	204	—	43	—	—	180	—	—	—	—	—
5	0.74	—	8	222	—	45	—	—	105	—	—	—	—	—
6	1.42	142	12	237	12.5‡	40	12.7	75	165	17.7	100	7.42	25	11.7
7	0.92	178	10	219	12.4‡	43	10.2‡	61	190	17.7‡	100	—	—	16.4
8	1.20	163	13	222	13.2	45	14.2	79	235	18.7	100	7.43	25	10.1
9	1.25	146	13	222	12.2‡	40	10.9‡	66	135	17.2‡	100	7.36	30	13.9
10	1.21	158	13	223	12.0	39	11.4	70	230	16.4‡	98	7.44	21	11.2
11	0.56	163	6	224	14.0	—	13.0	69	—	18.6	98	—	—	12.5
12	0.85	183	7	291	15.5	—	14.6	70	—	19.8	94	—	—	15.1
13	1.01	166	9	274	12.9	—	11.7	67	—	17.3	99	—	—	15.4
14	1.81	161	14	279	13.3	—	11.4	64	—	17.0	94	—	—	15.7
15	1.19	173	10	286	12.7	—	11.2	65	—	17.3	99	—	—	17.4
16	0.35	143	3	280	13.9	—	11.8	63	—	17.1	90	—	—	14.8
17	0.69	157	6	277	13.0	—	11.2	64	—	16.8	95	—	—	15.4

*Not synonymous with mixed venous blood (see flow circuit, Fig. 1). Includes all intracardiac return aspirated from the heart and returned to the machine.

†Values of pO_2 are those most representative of all values observed during perfusion (Cases 1-5) or those observed at time of withdrawal of samples (Cases 6-10).

‡Only single values for oxygen capacity and oxygen content were available in these cases; mean values based on two determinations were used in all the other cases.

intervals. In Cases 6 through 17, duplicate samples of blood were drawn at these sites 15 to 20 minutes after institution of perfusion and were analyzed for oxygen content, oxygen capacity, carbon dioxide content, and pH.

In the in vitro study, dog blood at 37° C. was desaturated in an isolated dog-lung preparation and pumped to an experimental oxygenator containing a single screen (25 cm. wide, 60 cm. high). A range of flow rates* (58 to 465 ml. per minute) or saturation (1 to 69 per cent) or both for the blood entering the oxygenator was obtained by altering the pump setting or by changing the gas mixture with which the isolated dog lung was being ventilated.

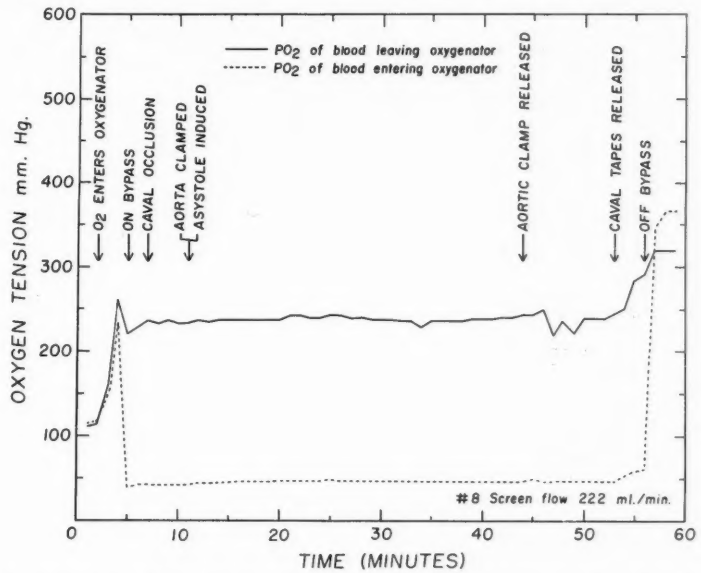

Fig. 3.—Oxygen tension in blood entering and leaving the oxygenator during whole-body perfusion in Case 8. See text for details.

RESULTS

The accompanying Table I summarizes all data obtained during the clinical perfusions. In Cases 1 through 11, the screen flow ranged from 204 to 237 ml. per minute per screen, averaging 220; in Cases 12 through 17, the screen flow ranged from 274 to 291 ml. per minute per screen, averaging 280. The hemoglobin content ranged from 12.0 to 12.5 Gm. per 100 ml. of blood, averaging 13.1. The remaining data in the Table will be considered in conjunction with Figs. 3 through 6.

The pattern of changes in oxygen tension observed in Case 8 (Fig. 3) was present in the 10 perfusions in which oxygen tension was measured. After filming, equilibrium was reached between the oxygen in the blood and that in the

*Flow rates in this study were the observed rates multiplied by $\frac{30}{25}$ in order to be comparable to the rates of the clinical perfusion, in which a screen 30 cm. in width was used.

air within the oxygenator. With the introduction of 98 per cent oxygen, the oxygen tension in the blood leaving the oxygenator began to increase. With the entry of desaturated blood from the patient, the oxygen tension in the blood entering the oxygenator decreased precipitously for 1 to 2 minutes and then became constant. During the 35 minutes of total bypass, the tension of oxygen in the blood entering and leaving the oxygenator was essentially constant. Release of the tapes on the venae cavae resulted in a reduction of the venous return to the machine. As a consequence, recirculation of blood through the

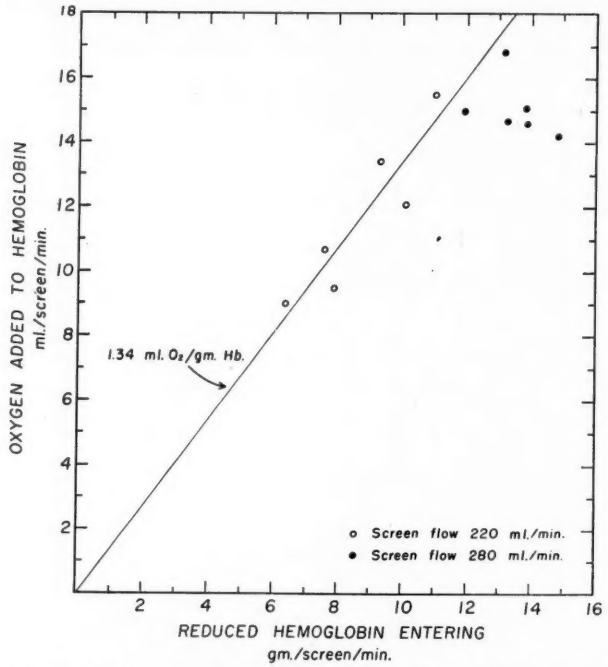

Fig. 4.—Performance of oxygenator screen at flows of 220 and 280 ml. per minute per screen. See text for details.

oxygenator occurred, with an increase in the tension of oxygen in the blood entering and leaving the oxygenator. While a range of oxygen tension was observed in blood entering (37 to 60 mm. Hg) and leaving (105 to 280 mm. Hg) the oxygenator in the 10 cases, the tension of oxygen in blood entering and leaving the oxygenator was always steady in each individual perfusion during the period of total bypass.

Fig. 4 presents the performance of the stationary vertical-screen oxygenator. The straight line indicates complete conversion of reduced hemoglobin to oxyhemoglobin. Points lying on this line indicate 100 per cent saturation of the blood leaving the oxygenator and were observed at screen flows of 220 ml. per minute; points below the line indicate desaturated blood leaving the oxygenator and were uniformly observed at screen flows of 280 ml. per minute.

At the former flow the rate of oxygen transfer was directly related to the rate at which reduced hemoglobin entered the oxygenator; at the latter flow, while both these rates were generally greater, the relationship between the two rates is not clear and is clarified in the in vitro study (Fig. 5). The amount of reduced hemoglobin entering the oxygenator was increased by keeping the actual rate of flow constant and increasing the degree of desaturation in the incoming blood and also by increasing the rate of flow while maintaining a fairly constant incoming saturation. Increasing the rate at which reduced hemoglobin entered the oxygenator by either maneuver resulted in an increase in the rate of oxygen transfer in the oxygenator.

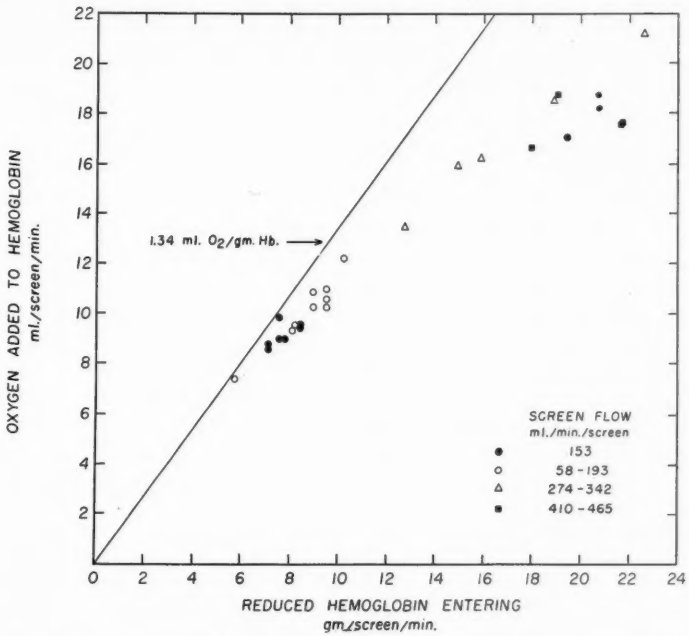

Fig. 5.—In vitro performance of the stationary vertical-screen oxygenator, using dog blood with an oxygen capacity of 18.9 volumes per cent.

Fig. 6 indicates the relationships in 12 patients between the observed rate of oxygen transfer in the oxygenator and the surface area of the patient. The mean of all observations was 131 ± 20 (S.D.) ml. of oxygen per minute per square meter of surface area; deviations from the mean amounting to 32, 47, and 22 ml. of oxygen in Cases 6, 7, and 8 were the major contributions to the magnitude of the standard deviation and are believed to be partly the result of sampling and analytic errors. The mean value of the basal oxygen uptake predicted for these 12 patients was 161 ml. per minute per square meter. The observed oxygen transfer was in one instance equal to and in 11 instances smaller than the predicted basal oxygen uptake.

COMMENT

During perfusion with an unchanging total flow, a steady state is one in which the oxygen content of the blood entering and leaving the oxygenator and the patient remains constant. It follows that oxygen levels in the patient remain steady and, further, that the oxygen transferred by the oxygenator is equal to the oxygen taken up by the patient. In the presence of a constant uptake of oxygen by the patient, the performance characteristics of the oxygenator determine if a steady state is achievable and also determine the actual levels of oxygen existing in the patient during the steady state.

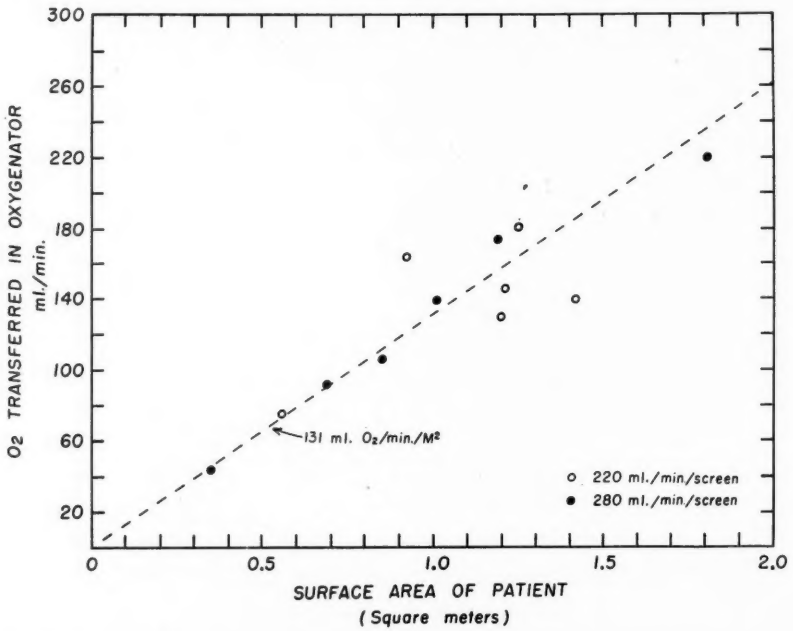

Fig. 6.—Relationship between surface area of patient and rate of oxygen transfer in the oxygenator.

Considerable evidence exists that a steady state was attained in these clinical perfusions. The constancy of the oxygen content in blood entering and leaving the oxygenator is believed to be indicative of the constancy of the oxygen content in blood leaving and entering the patient. (It is recognized that the exposure of blood to air in the venous reservoir and the return of intracardiac blood provide a basis for a possible discrepancy in actual contents.) The oxygen-tension data obtained at screen flows of 220 ml. per minute indicate that the tension of oxygen in the blood entering and leaving the oxygenator becomes steady soon after the institution of perfusion. Since no basis for a major change in the relationship of oxygen tension to oxygen content could be established, it was concluded that the levels of oxygen content were steady and,

further, that the oxygen uptake by the patient was steady. At flow rates of 280 ml. per minute, single observations were made 20 minutes after the establishment of the perfusion. It is believed that these measurements are also representative of the steady state for several reasons. First, in the aforementioned study, oxygen tensions became steady well before 20 minutes. The second reason is evident from the oxygen-transfer rates (ml./min./sq. meter), in which no difference is apparent in the rates calculated during periods of constant tension at flows of 220 ml. per minute per screen and in those calculated from single observations made 20 minutes after the establishment of perfusion at flows of 280 ml. per minute per screen. These observations further imply that the steady state at screen flows of the latter rate was arrived at without a change in the oxygen uptake by the patient. It will be remembered that these patients were perfused with incompletely saturated blood.

The performance characteristics of the oxygenator explain these observations. The rate of oxygen transfer in the oxygenator is related to the rate at which reduced hemoglobin enters the oxygenator. This relationship is such that, up to a certain rate of incoming reduced hemoglobin, the rate of oxygen transfer will be sufficient to saturate fully all reduced hemoglobin with oxygen. When the presentation of reduced hemoglobin exceeds this rate, the rate of oxygen transfer, while greater than that in the previous situation, will not be sufficient to saturate fully all entering reduced hemoglobin. Desaturated blood then will leave the oxygenator. The greater the degree by which this certain rate is exceeded, the greater is the degree of desaturation in blood leaving the oxygenator, but also the greater is the rate of oxygen transfer in the oxygenator. Therefore, a necessary consequence of operating the oxygenator in such a fashion that desaturated blood leaves it is that the arteriovenous difference across the oxygenator and, therefore, across the patient is widened, and actual levels of oxygen in the patient are lower.

SUMMARY

During normothermic perfusions at a blood flow of 220 ml. per minute per screen, the vertical-screen oxygenator, ventilated with 98 per cent oxygen and 2 per cent carbon dioxide, provided arterial blood with oxygen tensions of 105 to 280 mm. Hg and oxygen saturations of 98 to 100 per cent that remained constant throughout the perfusions. Increasing the screen flow to 280 ml. per minute per screen resulted in blood that had venous oxygen saturations of 63 to 70 per cent leaving the oxygenator with oxygen saturations of 90 to 99 per cent. The oxygen transferred by the oxygenator and utilized by the patients ranged from 99 to 178 ml. per minute per square meter of body surface. The characteristics of the oxygenator permit the attainment of a steady state by increasing its rate of oxygen transfer when presented with increased amounts of reduced hemoglobin per minute.

The participation in the in vitro studies of Mr. Richard E. Jones, of the Section of Engineering, and Dr. David E. Donald, of the Section of Surgical Research, and the technical assistance of Ruth Knutson and Richard Evjen are gratefully acknowledged.

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A ROTATING DISC BLOOD OXYGENATOR AND INTEGRAL HEAT EXCHANGER OF IMPROVED INHERENT EFFICIENCY

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THE ROTATING DISC, filming blood oxygenator has proved to be a very satisfactory instrument. In its most popular form (the variation by Kay and Cross[1]), it combines inherent simplicity with minimal trauma to the blood. Yet, satisfactory as they are, current forms of the disc oxygenator could be improved in two important respects: (1) it is desirable for the oxygenator to contain less blood while exposing a larger surface to oxygen, and (2) a larger heat-transfer surface is desirable for rapid cooling and warming of the contained circulating blood.

The currently popular type of 12 cm. diameter disc oxygenator is limited in its oxygenating efficiency largely by the occurrence of foaming if the discs are rotated too rapidly. It is restricted to a rather large contained volume of blood (in relation to the disc area exposed), mainly for the same reason, because foaming tends to occur if the level drops too low at normal rotational speeds, so that a rather large area of disc must be under blood at all times. This is most likely because at any point on the lower periphery of the disc where it is not immersed in blood, gravity is added to the centrifugal force and so tends to cause splashing when the blood level is low. Finally, the oxygenator is limited in its ability to transfer heat by the rather small area of blood in direct contact with the casing which can be warmed or cooled.

It is obvious that the oxygenating efficiency of a disc oxygenator is related to the area of disc submerged in the blood trough compared with the wetted area of the disc exposed to oxygen. Therefore, a disc oxygenator is most efficient (as measured by ratio of oxygenating surface to contained volume) if the disc is very large and dips only slightly into the blood trough (Fig. 3). However, the practical size of the disc is limited by the limit on the linear speed of the disc rim due to foam formation at high speeds.

Experimentally, it can be shown that when discs rotate while dipping into blood a higher rim-speed can be achieved without foam formation if the clearance

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between disc edges and casing is very small, so that a continuous meniscus of blood is continually present between disc and casing all around its periphery. If such a meniscus of blood is maintained all around the disc, then obviously the whole adjacent interior cylindrical surface is wet with non-stagnant blood and thus can be used as a heat-transfer surface.

Based on these principles, an oxygenator has been designed which incorporates marked improvements in oxygenating efficiency and heat-transfer characteristics over current disc oxygenators.

11·8 cm. OXYGENATOR GEOMETRY

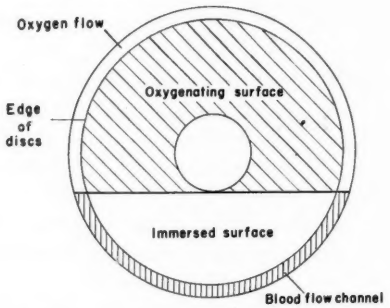

Fig. 1.—Diagram of the geometry of an 11.8 cm. disc oxygenator.

DESIGN DESIDERATA

Disc oxygenators of 11 to 12 cm. disc diameter are presently widely used, and unless significant improvements on their performance could be realized the development of a new one would be unwarranted. Consequently, emphasis is laid in this report on direct comparisons with a standard 11.8 cm. disc oxygenator.[1]

Geometry of the 11.8 Cm. Oxygenator.—A 21 inch long oxygenator with one hundred 11.8 cm. discs has a priming volume of 2.5 liters and, thus primed, an oxygenating surface of 1.33 square meters (per revolution), which is the maximum obtainable. In use, the discs are usually immersed to 4.1 cm., which is 69.2 per cent of their radius. There is an 0.56 cm. clearance between the periphery of the disc and the cylinder or casing, through which blood and oxygen can flow. The recommended maximum rotation speed is usually 120 r.p.m. The geometry is shown, full size, in Fig. 1.

Geometry of Our New Oxygenator.—In order to improve the ratio of oxygenating surface to priming volume it is clear, as already mentioned, that the discs must be immersed to a much smaller fraction of their radius, so that only a narrow annulus becomes wetted. This is illustrated in principle in Fig. 2 (assuming the same diameter discs were used).

Since the immersed surface (plus the cross-sectional area of the blood flow channel) is proportional to the priming volume, it is obvious by visual comparison between Figs. 1 and 2 that the *ratio* of oxygenating surface to priming

volume is much better in Fig. 2 than in Fig. 1; they are, respectively, 1.15 and 0.58.* However, the oxygenating surface is considerably smaller than in Fig. 1, 0.88 square meters as against 1.33 square meters. Therefore, to obtain adequate oxygenation with this more efficient geometry we must increase the diameter of the discs. A diameter of 8¼ inches (21 cm.) is a convenient compromise. However, whereas centrifugal force acting on blood at the periphery of an 11.87 cm. disc rotating at 120 r.p.m. is 0.96 g., on a 21 cm. disc it is

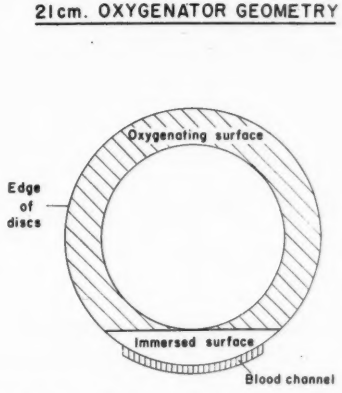

Fig. 2.—Diagram of the geometry of our new 21 cm. disc oxygenator.

1.7 g. The tendency for droplets to be flung off the discs and splash against the cylinder wall is therefore nearly doubled with the larger disc, with consequent danger of foam formation. We have reduced this danger by reducing the clearance between the discs and the cylinder wall to 0.016 inches, which is small enough to be easily and consistently spanned by the centrifugally formed blood meniscus. The blood then touches both disc and casing all the way around, and foam formation is much reduced.

Since this arrangement leaves room for neither blood nor oxygen to flow axially through the oxygenator, other provisions must be made. We have provided blood flow by a longitudinal channel at the bottom of the cylinder, the cross-section of which is a concentric annular segment 0.63 cm. deep, subtending an angle of about 64 degrees. This channel has a cross-sectional area equivalent to a 1.22 inch diameter circle, and will permit a 4 liter per minute gravity flow under a head of 2 inches.† (This, therefore, will be the order of maximum difference in level between the entry and discharge ends of the unit.)

Oxygen flow is made possible by one ⅝ inch diameter hole in each disc near the shaft. On assembly each hole is oriented at 180 degrees to those in adjacent discs, so as to encourage mild oxygen turbulence between them.

Other important considerations in design are applicability of cleaning techniques, and ease in sterilization. The present apparatus has therefore been designed and built entirely of parts which can be autoclaved, and access for cleaning is provided to every place touching blood. Cracks and recesses hard to find with a brush have been avoided.

*The units used are square meters per revolution (100 discs) divided by liters. This ratio may be regarded as a measure of "efficiency."

†Obtained by actual test.

Detailed Design Specifications.—

1. The main cylinder and discs are made of stainless steel.
2. The end-covers are made of transparent Kel-F-plastic, reinforced with aluminum, which latter does not come in contact with the blood.
3. The blood inlet and outlet are vertical, below the discs.
4. The blood outlet is provided with an anti-vortex baffle.
5. A jacket is provided for hot or cold water circulation to provide temperature control.
6. A two-stage rubber belt speed-reducing drive with motor attached to the unit are provided, so that the unit can be freely suspended and continuously weighed for accurate volume control. A voltage generator is similarly attached for speed measurements.
7. Electric light bulbs are mounted inside end-covers to facilitate observation of blood levels.
8. A clip is provided at the output end of the oxygenator for a photocell level-sensing device.

CLEANING AND MAINTENANCE

The procedures for cleaning and maintenance of an oxygenator are of crucial importance. Our entire unit can be disassembled after use, and each part individually scrubbed and treated. The nearer the entire unit can be made chemically clean the better. As a minimum, every part which can possibly touch blood should be scrubbed individually with appropriate detergent, then rinsed long and hard. All parts should then be dried and coated with baked silicone before each use. Several commercial silicone preparations are satisfactory; we have used an acetone solution of Dow-Corning DC1107. All parts are dipped in this solution, and then baked at approximately 100° C. for one hour.

Ideally, the previous silicone coating should be removed after each use, and all organic matter should be taken off by strong acid or a strong oxidizing agent. Where cleaning and maintenance are to be done in the hospital, complete disassembly with attention to each part may be necessary. However, where it is possible to handle washing in bulk, and where strongly caustic solutions can be handled safely in larger tanks, the whole assembly of discs-on-shaft can be handled as a single unit without taking it apart.

By an arrangement with a local commercial laboratory, we have found it convenient to have the detailed cleaning take place outside the hospital. We will describe our technique as it has been found quite satisfactory, but a similar routine could easily be set up in many large hospitals, or modified by individual circumstances. Our procedures as described were planned with a view to: (a) transfer of a high proportion of the cleaning labor load from the hospital staff to an outside commercial laboratory; (b) reduction of total man-hours of cleaning per perfusion; (c) destruction of all pyrogenic substances; and (d) removal after each perfusion of the silicone coatings (which otherwise accumulate) and recoating with a fresh surface. We have accomplished these aims in the following manner.

For an average of five perfusions per week, we have available two cylindrical stainless steel oxygenator casings and eleven disc-shaft assemblies. The disc-shaft assemblies are processed in rotation outside the hospital.* The discs are never disassembled from the shafts and handled singly, but each shaft-disc assembly is processed as a unit. Immediately after each perfusion the oxygenator is rinsed out with water and detergent, and the shaft-disc assembly is then removed from the casing. To facilitate transport it is mounted in a light stainless steel cradle which forms the lid of a light galvanized steel box for protection in (truck) transport. After insertion in this box the assembly is autoclaved (for the protection of the processors) and shipped to the processor. Processing is done there by immersion in appropriate liquids without removal from the cradles.

The treatment consists of:

1. Immersion in 5 per cent potassium hydroxide in alcohol at 60 to 70° C. This removes the silicone coating.
2. Rinsing in water.
3. Immersion in concentrated (commercial) nitric acid. This cleans the discs, oxidizes all organic materials and so destroys pyrogens.
4. Rinsing in distilled water.
5. Drying.
6. Silicone coating by immersion in standard acetone solution of silicone DC1107.
7. Drying and baking.
8. Final spraying with distilled water (pyrogen-free).
9. Re-insertion in box and shipment to hospital.

The treatment of the casing consists at present of a scrubbing with water and detergent followed, after rinsing by flooding with a strong (0.5 per cent) solution of potassium permanganate. For the sake of consistency it is intended to substitute treatment with nitric acid. No silicone coating is applied to the casing, since its surface constitutes only a small fraction of the total wetted surface. Stainless steel endplates are provided with trunnions, permitting the casing to be one third filled with nitric acid, and swung so that the entire surface is treated. After a final rinsing with distilled water the casing is ready to receive a shaft-disc assembly from the revolving stock kept in reserve at the hospital.

When fully assembled, the oxygenator is autoclaved not more than 24 hours before perfusion. No antifoam is used. The approximate disposition at any one time of the eleven shaft-disc assemblies is as follows: in transit, 4; in process, 4; in use, 1; in reserve, 2, which makes a total of 11.

This type of rotation of several internal assemblies is efficient when a large number of perfusions are performed, and cleaning is to be done by "mass production." However, it is reasonably easy to carry out one perfusion daily

*Cutter Laboratories, Berkeley, California.

using one casing and two disc-shaft assemblies. In this case, cleaning must be done inside the hospital by a technician assigned especially to this job. One disc-shaft assembly is cleaned while the other is being used. The casing (which is quickly cleaned) is finished immediately after the perfusion of the day. Then the clean disc-shaft assembly is slid into it, and the whole unit is sent to the autoclave to be sterilized for the next morning's run.

PERFORMANCE

A. *Theoretical.*—Fig. 3 shows the variation of priming volume and oxygenating surface with blood level (above the lower horizontal tangent to the discs) for both an 11.8 cm. diameter 100 disc oxygenator and our 21 cm. 96 disc unit.

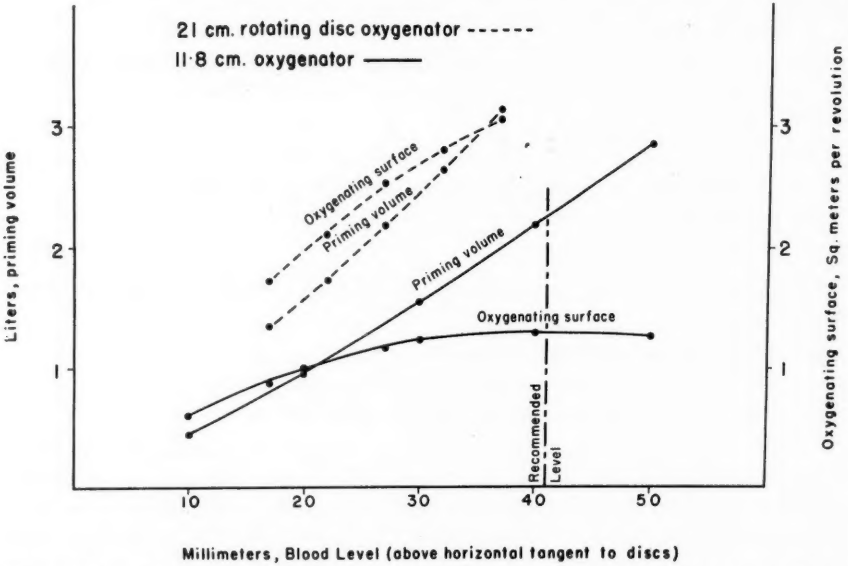

Fig. 3.—Diagram comparing oxygenating surface and priming volume at varying blood levels in both the 11.8 cm. and 21 cm. disc oxygenators.

The values are obtained by geometric computation—the priming volume graphs therefore do not take account of the volume of blood adhering to the discs above blood level; tests have shown the correction to be of the order of 10 per cent. It will be noted that the maximum oxygenating surface (per revolution) of the 11.8 cm. diameter unit is 1.33 square meters, compared with 2.55 square meters for our 21 cm. diameter unit at the same priming volume (2.25 liters). The latter figure is not a maximum. If a priming volume of 3 liters (plus correction for wetted oxygenating surfaces) is accepted, the oxygenating surface will be 3.0 square meters per revolution, or 2.25 times the maximum obtainable with the 11.8 cm. diameter disc machine.*

*In our 21 cm. unit there is an additional 0.3 square meters of static oxygenating surface provided by the (continuously wetted) cylinder wall. Since, however, the rate at which this blood film is renewed cannot be calculated, this surface has been ignored.

The variation of oxygenating surface with priming volume is shown in Fig. 4 for both oxygenators. (Note: the ordinate units in this graph are square meters per minute at 120 r.p.m.) Fig. 5 shows the variation of "efficiency," i. e., ratio of oxygenating surface in square meters per revolution to priming volume in liters against oxygenating surface.

B. *Practical.*—The oxygenator just described* has been used for perfusion of 22 patients with congenital and acquired heart disease at the San Francisco-Stanford Hospital. Several patients were perfused for periods of over one

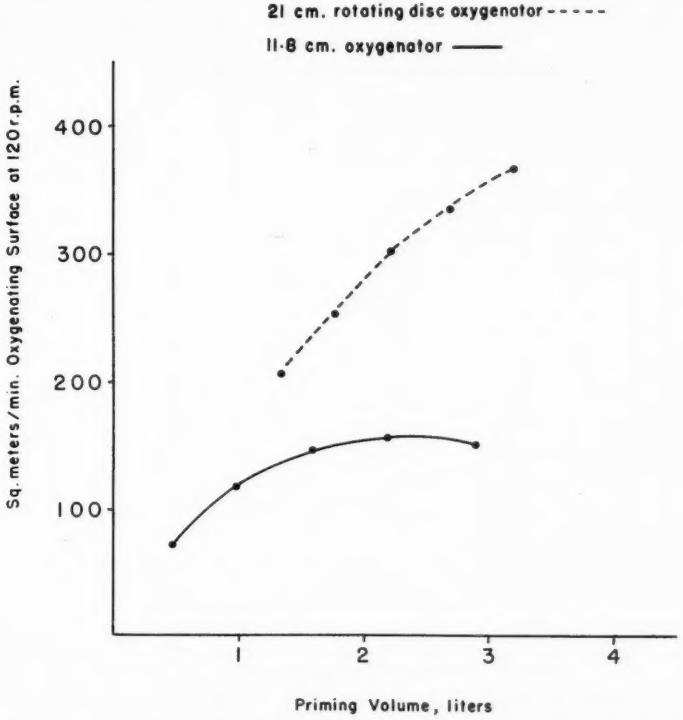

Fig. 4.—Diagram comparing oxygenating surface at varying priming volumes in both the 11.8 cm. and 21 cm. disc oxygenators.

hour. Two severely ill patients (with tetralogy of Fallot) were on total perfusion for 80 minutes and 100 minutes, respectively, and both convalesced rapidly, with almost no postoperative fever or other difficulty. Hemolysis under operating room conditions has been unmeasurable, because the major cause of hemolysis is the suction of blood from the open heart by the "coronary sucker," and hemolysis caused by the oxygenator has been too small in comparison to measure separately. In one 25-minute period of full perfusion in an adult, during which the coronary return suction system was not used, the plasma

*Manufactured by Hallikainen Instruments, Berkeley, California.

hemoglobin at the end of the 25-minute period was less than at the beginning of the period. The largest patient perfused weighed 170 pounds. There has never been difficulty in maintaining arterial saturation over 90 per cent.

The apparatus, including all tubing, filter, etc., is easily primed for an adult with six units (3,000 c.c.) of heparinized blood, much less if a small child is the patient.

It is our clinical impression that the series of patients perfused with this oxygenator have been less sick in the postoperative period than patients perfused with previous machines. It is impossible to make exact comparisons, but certainly fever used to be common in the first postoperative days, and has become

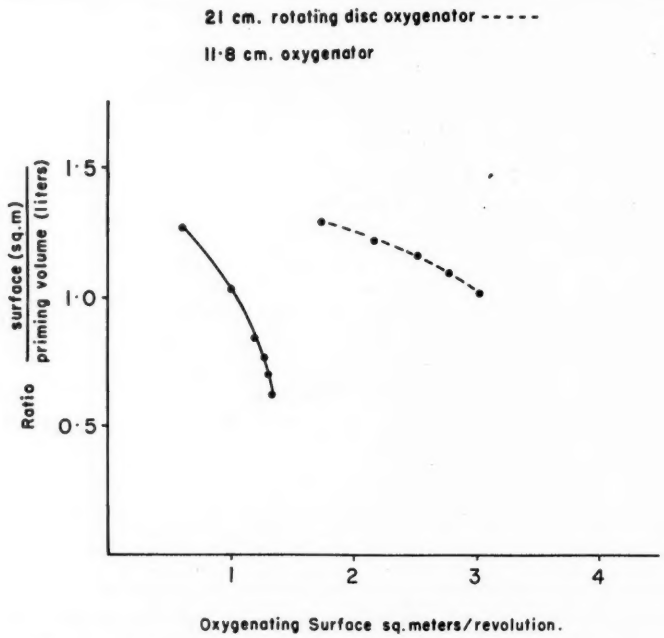

Fig. 5.—Diagram showing surface to priming volume ratio against varying oxygenating surfaces in both the 11.8 cm. and 21 cm. disc oxygenators.

very much less common, and, when present, is less severe. We have the clinical impression that pulmonary symptoms are also less, and that the postoperative roentgenograms are clearer.

Foaming in the oxygenator has never occurred, though no antifoam has been used. There has been no severe postoperative bleeding, and the bleeding in general has been as little as or less than that when previous machines were used.

All patients have had their body temperatures electively lowered to 32° C. at least, many to much lower temperatures. The data on type of induced hypothermia are extensive and must form the subject of a separate communication, but it is appropriate here to stress the ease with which hypothermia may be

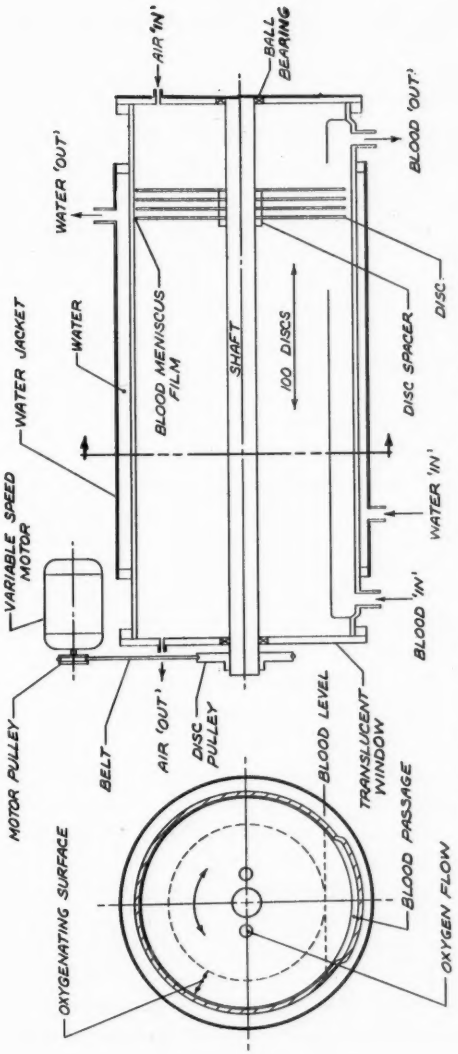

Fig. 6.—Sectional diagrammatic sketch of 21 cm. disc oxygenator.

induced, and then the patient rewarmed, without the use of a separate blood heat-exchanger. Body temperatures (in adults) have been routinely lowered at the rate of roughly 0.67° C. per minute, and raised at the rate of roughly 0.5° C. per minute. This represents heat transfer at a rate of over 50 kilogram-calories per minute. Much faster cooling and rewarming rates are possible in children.

PUMP AND CONTROL APPARATUS

The foregoing description has applied to the oxygenator alone. Obviously an oxygenator needs a pumping and control system, but this oxygenator could be adapted to many existing pumping systems. In our own use we have incorporated it in a chassis which we will describe.

The oxygenator (with its water-jacket, disc rotation drive, light source, and generator-tachometer) is suspended from two steel bending beams which are adapted with Baldwin-Lima-Hamilton SR4 strain gauges to sense weight. Weight of the unit (with its contained blood) is read out on a visible indicator (Minneapolis Honeywell) and also fed to a control system linked to the drive of the arterial pump. The unit can then be adjusted to sense the volume of blood in the oxygenator within 10 or 20 c.c. of blood, and to adjust automatically the speed of the delivery pump (the arterial pump) to maintain a constant volume of blood in the artificial lung. This automatic control can be bypassed with a manual control as desired, but it makes it possible for the operator to maintain very strict sensing of the total blood volume of the patient, and also greatly reduces the danger of air embolism to the patient (from the blood level in the oxygenator accidentally dropping too low). We have used Gibbon-type De Bakey pumps for both the arterial delivery and intracardiac suction, and we incorporate a filter and air-trap in the delivery system.

To reduce as much as possible the chance for human error we have incorporated also several safeguards, many of which we had found useful with previous oxygenators.[2] These include:

1. An audible signal (fed by photocell) if the blood level in the oxygenator drops below a set level.
2. Automatic arrest of the arterial pump if the blood weight drops below a preset amount.
3. An electrically lighted plastic window for observing blood level.
4. An automatic audible warning if the line pressure in the arterial delivery line rises above 300 mm. Hg, with automatic cut-out of arterial pump.
5. A manometer indicating delivery-line pressure.
6. A tachometer showing speed of oxygenating disc shaft.
7. An alternate electrical control system (direct current) for use in case of alternating current line failure.
8. Provision for manual pumping (with detachable handle) in case of mechanical or other failure.
9. Two electric thermometers for blood and water-jacket temperature.

SUMMARY

A new disc-type blood oxygenator has been described which exposes a larger area of oxygenating surface compared with the volume of contained blood than previous disc oxygenators.

Through its inherent design, the oxygenator functions also as a highly efficient heat exchanger.

Details of design, performance, and maintenance are presented.

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A MODIFICATION OF THE CLOWES MEMBRANE LUNG

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NO CLINICAL substitute for the normal lung is ideal. In the laboratory, the homologous lung approaches perfection, but unfortunately it cannot be used clinically. Heterologous lungs and all presently available machines are imperfect for one or more reasons: they are emboli-prone, trauma is too great, there is an element of unreliability, priming volume is excessive, they are too complicated, they are too expensive, or they are simply too tiresome to assemble, sterilize, or operate. Probably no real solutions to the problems are possible where gas and liquid phases are not clearly separated, as by a membrane. With the membrane lung, practically all of the present defects can be obviated to some degree when very large flows are not required. Some difficulties, such as complicated monitoring, can be eliminated entirely. We believe it is important to present our modification of the Clowes membrane lung[1, 2] since it can be readily constructed and used by any interested research worker or clinician. With more general experience will come an appreciation of its advantages. Attention to the advantages of the membrane lung should permit production of a satisfactory disposable unit.

A mechanical lung substitute should be called an artificial lung and not an oxygenator, since it must provide adequate carbon dioxide elimination as well as oxygenation (Table I). For every 5 c.c. of oxygen taken up by the blood, 4 c.c. of carbon dioxide must be removed. Failure to maintain a proper balance leads to an unphysiologic pH and may be quite dangerous. The functional unit of the human lung is the alveolus and there is considerable intellectual appeal and practical advantage to the construction of an artificial lung which comprises the elements of air sac, membrane, and capillaries. It is important to realize that one is endeavoring to substitute only for the basal functions of the normal lung and that for only a limited time. These basic concepts set the stage for the development of a membrane lung.

The necessary physical condition for a balanced function of the artificial lung are a pO_2 above 80, a pCO_2 below 50, and a pH of about 7.3 to 7.4. In order to understand the requirements for such a lung, the behavior of oxygen and carbon dioxide in blood and in relation to the best available membranes

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TABLE I. HUMAN LUNG

Functions	*Unit*	
Oxygenate blood Eliminate carbon dioxide Maintain pH	Alveolus	Air sac Membrane Capillaries
	Range	
Ventilation	5 to 100 L./min.	
Blood flow	3 to 30 L./min.	
Gas exchange	200 to 2,400 c.c./min.	

must be known. In solution, these two gases behave quite differently. Oxygen is relatively insoluble, practically all being carried in chemical combination with hemoglobin. Since the diffusion of a gas through a liquid is directly proportional to its solubility, oxygen diffuses very slowly and a thin film is necessary for adequate oxygen exchange. Carbon dioxide is comparatively very soluble and diffuses about 30 times as fast as oxygen, so that the thickness of the blood film has relatively less bearing on carbon dioxide exchange. Now, the best available membrane for oxygen and carbon dioxide transfer is Teflon. Because of strength limitations, the thinnest useful membrane is $\frac{1}{2000}$ of an inch. The transmission of oxygen through such a membrane has been measured with the platinum polarograph[3] and the results confirmed using a diffusion chamber.[5] The relative diffusibility of oxygen and carbon dioxide are illustrated in Table II. Although carbon dioxide diffuses much more readily than oxygen, the physiologically tolerable pCO_2 results in a relatively unfavorable diffusion rate. The conclusions resulting from study of the best available membrane and the relative behavior of oxygen and carbon dioxide in blood follow.

TABLE II. TRANSMISSION OF OXYGEN AND CARBON DIOXIDE THROUGH 0.0005 IN. TEFLON MEMBRANE AT BODY TEMPERATURE IN C.C./M.²/MIN.

	AS GAS AT ONE ATMOSPHERE PRESSURE	THEORETICAL IN MEMBRANE LUNG*	ACTUAL IN MEMBRANE LUNG	PER CENT EFFICIENCY OF LUNG
Oxygen	45	40	10	25
Carbon dioxide	120	8	8	100

*PO_2, 690 mm. Hg; pCO_2, 50 mm. Hg.

TEFLON MEMBRANE LUNG

A. Carbon dioxide is very soluble and diffuses rapidly, therefore (1) the membrane and permissible pCO_2 determine CO_2 elimination, (2) because pCO_2 must be low, CO_2 elimination is limiting factor in lung function, and (3) it dictates the necessary membrane area.

B. Oxygen is one thirtieth as soluble and diffuses slowly, so that (4) oxygenation depends on blood film thickness and transit time and hence on lung design, (5) it is relatively independent of the membrane using reasonable film thicknesses, and (6) with adequate CO_2 elimination, there is considerable oxygenation reserve. There appears, therefore, little present need to strive for maximum efficiency of oxygenation.

Given these facts, we have constructed a modification of the Clowes membrane lung which is somewhat simpler, much less expensive, and has approximately one half the bulk. It is quite interesting to compare the dimensions of this apparatus with the dimensions of the normal human lung (Table III). Such a lung can be built in a few days using readily available tools and materials. No great precision is required in the construction. The finished apparatus can be cleaned and put together in less than an hour. Almost everything that comes into contact with the blood is disposable. Chemical or standard steam autoclaving is possible and the machine may be set up and kept ready on the shelf. The Teflon membrane lung works best at body temperature. However, it loses efficiency very little when cooled and will perform satisfactorily at 20° C. or lower. The main problem in cooling is that the pCO_2 drops rapidly as the solubility of CO_2 increases, leading to relative CO_2 retention.

TABLE III. COMPARISON OF MODIFIED CLOWES AND HUMAN LUNG

	HUMAN LUNG (BASAL)	MEMBRANE LUNG
Gas	*Air*	*Oxygen*
Average O_2 gradient	45 mm. Hg	650 mm. Hg
Average CO_2 gradient	3 mm. Hg	45 mm. Hg
D CO_2/D O_2*	15	15
Blood film thickness	0.01 mm.	0.24 mm.
Transit distance	0.75 mm.	24 cm.
Transit time	0.75 sec.	60 sec.
Blood flow/M.²/min.	25 c.c.	100 c.c.
Blood volume/M.²	2.5 c.c.	120 c.c.
Total volume/M.²	45 c.c.	1,350 c.c.
O_2 and CO_2/M.²/min.	2 c.c.	10 c.c.

*D = c.c. diffused per millimeter of mercury pressure per minute.

Data from animal experimentation are shown in Table II. Note that the efficiency of carbon dioxide elimination approaches 100 per cent, while the efficiency of oxygenation is in the neighborhood of 25 per cent. This confirms

TABLE IV. MEMBRANE LUNG*

	BEFORE PERFUSION RECTAL TEMP. 98° F.	PRIMING BLOOD	AFTER PERFUSION RECTAL TEMP. 97° F.	FOUR HOURS AFTER PERFUSION
White blood cells	7,500	6,950	16,200	11,450
Platelets	318,000	208,000	317,000	480,000
Hematocrit	31	46	42	40
Serum hemoglobin	0 mg. %	24 mg. %	56 mg. %	36 mg. %
pH				
Venous	7.23		7.24	
Arterial	7.24		7.22	
O_2 % Sat.				
Venous	47		36	
Arterial	83		98	
O_2 Vol. %				
Venous	8.8		6.1	
Arterial	15.3		16.4	
CO_2 Vol. %				
Venous	54.2		55.3	
Arterial	44.5		45.9	

*Thirty minutes regional perfusion, 450 c.c. flow per minute, 3.6 M.² of 0.0005 in. Teflon.

the theoretical predictions. A favorable ratio of blood gases is provided and the pH is held within physiologic limits, provided the proper membrane size and flow are chosen. The satisfactory results of a 30-minute regional perfusion of the pelvis for treatment of metastatic carcinoma with nitrogen mustard are shown in Table IV.

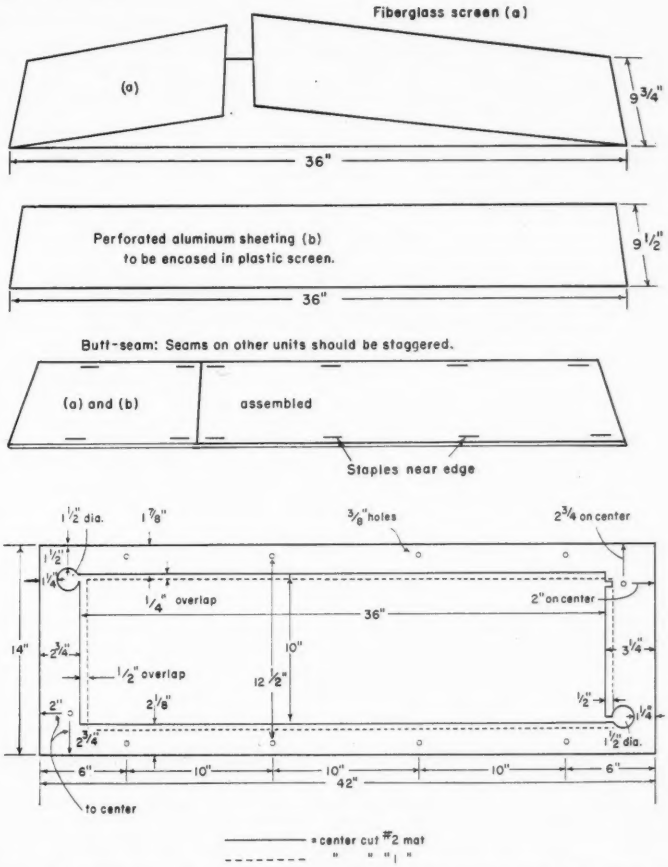

Fig. 1.—The dimensions of an individual gasket are illustrated and all except the outside measurements are important (see text). The inserts are fashioned from perforated aluminum sheeting (Lincane, 0.025 inch thick). Application of the Fiberglas screen is now done with a longitudinal butt joint. The result is better if the screen is sewed rather than stapled.

In summary, the advantages and disadvantages of the Teflon membrane lung are shown in Table V.

CONSTRUCTION

The key to simple construction of one of these units is preparation of an accurate gasket made of 1/16 inch rubber matting. This gasket determines the dimensions of all of the other parts of the apparatus. This initial pattern should be prepared as shown in Fig. 1 (without cutting out the central rectangular

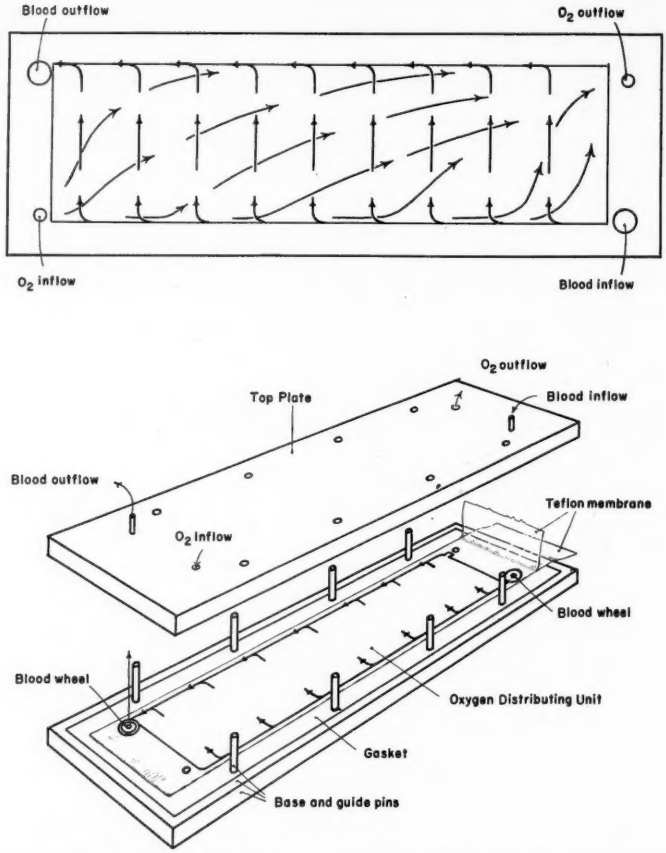

Fig. 2.—The general layout of the artificial lung, together with the flow pattern for gas and blood, is illustrated. Blood flow is between the layers of Teflon membrane while oxygen flow is through the porous inserts of Fiberglas and aluminum. The gas and blood are preferably run countercurrent.

TABLE V

ADVANTAGES	DISADVANTAGES
Simplicity of regulation	Only commercial one is expensive*
Safety	Disposable Teflon is expensive
Trauma	Once set up capacity is not adjustable
Emboli	
Predictable control O_2, CO_2, pH	
Relatively constant volume	
Easy to clean	
Functional parts disposable	
Relatively small priming volume	
No antifoam	

*Mark Co., Randolph, Mass.

hole). The outside may be cut quite roughly, but the various holes should be made with great care. Standard cork borers are used for the smaller ones, while the 1½ inch diameter holes are cut using a borer made from thin-walled brass pipe. The four small holes along each side determine the position of the guide pins in the base of the lung (Fig. 2). The central rectangles are staggered to allow support for the central inserts shown in Fig. 3, so that there are two types of mats. Further details of construction are shown in the accompanying

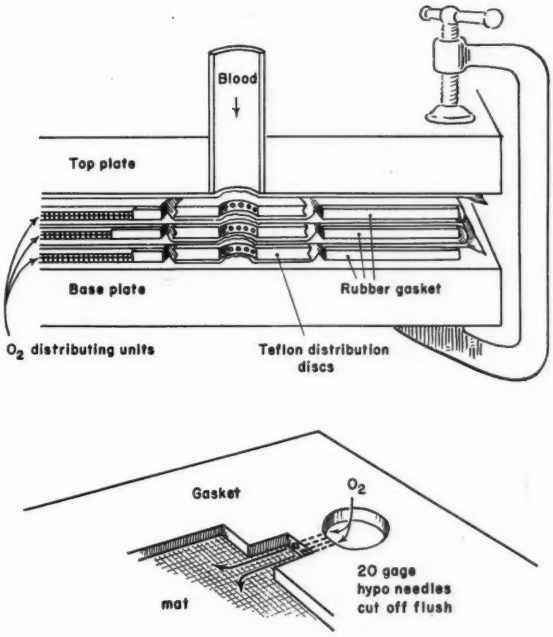

Fig. 3.—The method of blood and oxygen distribution is illustrated. The needles used for oxygen distribution are cut off simply by bending with a pair of pliers. The blood distributing discs are fashioned from 1/16 inch thick Teflon with the cutter used to make the 1½ inch holes in the gaskets. Six radial holes are made in each disc, using a drill about 3/64 inch in diameter. This is most easily done by holding the disc against a stationary drill, such as a drill press, and guiding the drill by keeping one finger on each side of the hole so that lack of alignment can be detected and corrected quickly. After drilling the radial holes, about ⅛ inch is cut from the circumference of each disc with a sharp knife or a second brass cutter. A central hole ½ inch in diameter is then cut. If the drilling is done as the last operation, a burr will result. Pairs of blank discs in several thicknesses are also required (see Assembly). A convenient inlet or outlet tube may be made from a piece of Tygon with a flared end that fits into a blank disc which must then have a ¾ rather than a ½ inch central hole.

figures. Acrylic plastic is very satisfactory for the top and bottom plates when chemical sterilizing is available, but if ordinary autoclaving is to be employed, the plates should be made of metal. The original pattern should be kept intact so that additional gaskets can be made when desired. Required materials and the approximate cost are shown in Table VI.

TABLE VI. MATERIALS REQUIRED FOR CONSTRUCTION OF A 10 SQUARE METER TEFLON MEMBRANE LUNG

2 sheets Plexiglas (15 in. by 42 in.)	$ 30.00
24 3 in. C clamps	24.00
14 yards 1/16 in. by 36 in. rubber sheeting	33.00
8 36 in. by 36 in. perforated aluminum sheets	18.00
30 yards 24 in. Fiberglas screen	7.00
1 square foot 1/16 in. Teflon	4.00
2 feet 3/8 in. aluminum rod	1.00
Total	$117.00
Each additional mat (0.45 square meter membrane)	2.50
0.0005 in. Teflon* membrane per square meter	4.00

*Dilectrix Corp., Farmingdale, L. I.

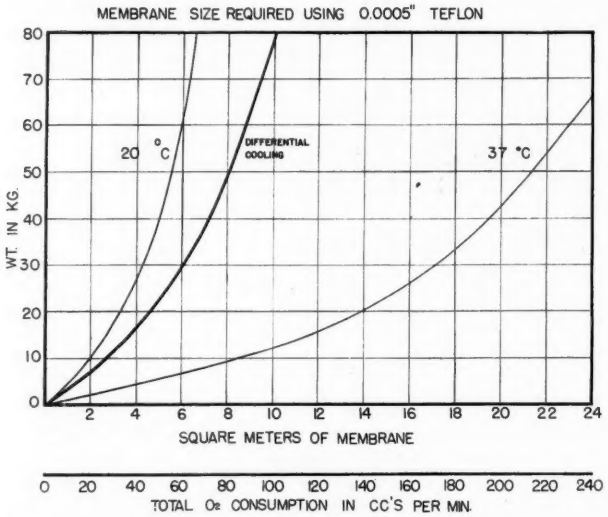

Fig. 4.—The required membrane size is based on the ability of the membrane to transmit carbon dioxide. The amount of membrane indicated provides some oxygenation reserve. This chart may be used for a variety of purposes including determining the requisite blood flow. A flow of 100 c.c. per meter of membrane should fully oxygenate blood even when less than 50 per cent saturated. These flows should prove satisfactory although they are somewhat less than so-called "full flow." (From Peirce et al., J. Tennessee State M. A. 52: 39-44, 1959.)

OPERATION

I. *Assembly.*—

A rubber mat and an insert are placed on the base plate of the lung. Two layers of Teflon membrane are carefully rolled on top of these. Blood distribution discs are placed between the layers of the membrane. A second mat and insert are now placed on top of the Teflon, with care to use a mat that is out of phase with the first one. The process is repeated until the requisite number of meters have been applied (Fig. 4).* The utilization of differential cooling as previously reported will greatly decrease the necessary membrane area.[4] No membrane is placed over the top mat and insert and instead of using an ordinary

*Each mat has an area 10 per cent less than 0.25 meters. For each mat two layers of membrane are used. Roughly, therefore, there is one meter of membrane for each two mats.

blood distribution disc, a blank is placed in the large hole of the top mat. Care should be taken that the stacks of distribution discs are the same height as the pile of gaskets, and this can be brought about by having blanks of several thicknesses (produced by sanding down ordinary blanks). An actual cautery is used to perforate the membranes so that gas and blood can circulate. This is best done before applying the top plate. The 24 C clamps are placed symmetrically and tightened firmly. The lung is then tested by placing it on the floor and running normal saline solution into the inlet from a height of 1.5 to 2 meters. As soon as saline appears at the outlet, this is clamped. The saline

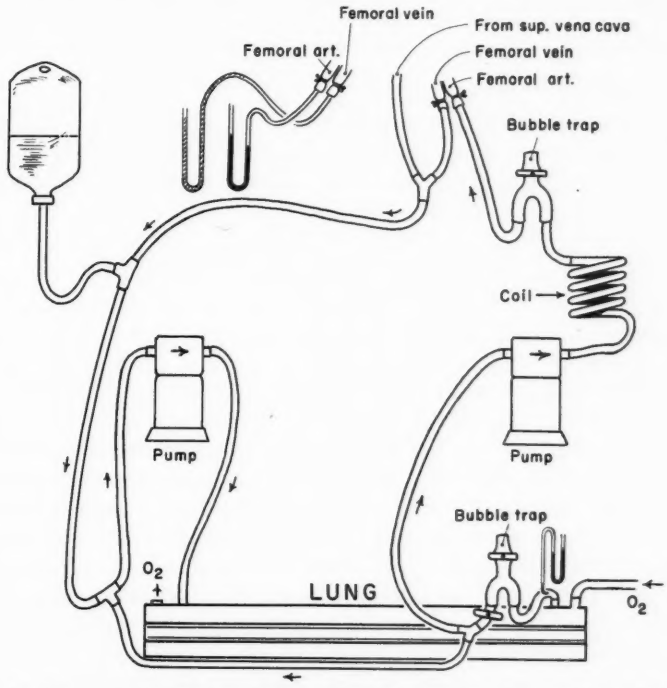

Fig. 5.—The circuit illustrated provides everything essential for a safe perfusion. Monitoring devices, a filter, etc., may be added as desired. Note the lack of control devices. (Modified from Peirce et al., J. Tennessee State M. A. 52: 39-44, 1959.)

is allowed to run until it slows down greatly or stops. While this is being done some gas is blown through the lung so that any leakage will be apparent by liquid coming out of the oxygen outlet. Using saline there is practically always slight leakage and a continued drip of up to at least 200 drops a minute is permissible and does not imply any significant blood leak. After testing, the lung is drained by standing it on end.

II. *Circuit.*—

A very effective circuit is illustrated in Fig. 5. Two pumps of any satisfactory variety are needed. The lung may be at the same level as the pumps

or below, and it makes very little difference. The two bubble traps are necessary for proper priming. They are very simply constructed from ¾ inch Tygon T's. When the blood enters the bubble trap it slows because of the increase in caliber. This, together with the effect of gravity, provides excellent removal of any free bubbles. A stainless steel filter has been used in human beings but not in animals, and we are not convinced that such a filter is necessary or desirable, as very little material tends to collect in it. Temperature is controlled by means of a stainless steel coil or, more recently, by two stainless steel plates held 1/16 inch apart by a gasket. The heat exchanger can be placed in ice water for cooling or in a warming bath at any temperature up to approximately 40° C. An area of 0.1 meter is entirely adequate for a flow of 1,000 c.c. per minute.

III. *Sterilization.*—

In the research laboratory, although the tubing of the pump circuit has been sterilized with aqueous Zephiran, we have not sterilized the lung itself. For clinical work, we have fortunately had available an ethylene oxide autoclave. The lung and the entire circuit are sterilized as a unit and kept available for use. Steam autoclaving should be entirely satisfactory if metal is used for the lung frame.

IV. *Priming.*—

Using the recommended outlet pressure of about 20 mm. Hg, each meter of lung area requires approximately 120 c.c. of blood to prime it. With abnormally high outlet pressures up to 150 mm. Hg, the priming volume may be more than doubled. The outlet pressure may be monitored with a mercury manometer and controlled with a screw clamp on the outflow limb of the bubble trap. A simple alternative method of pressure control permits elimination of the manometer. The bubble trap is placed about 25 cm. above the outlet of the lung. The screw clamp on its outflow limb is adjusted so that the outflow pressure just supports this 25 cm. column of blood.

The external circuit, consisting of the venous line, shunt, arterial pump, and the remainder of the arterial line, is closed by connecting the venous and arterial limbs which will later be separated and attached to their respective cannulae. In patients, this can be done most conveniently by using a fresh continuous loop of tubing which is then cut and attached to the cannulae after the circuit has been primed. The venous reservoir is placed at the height of the bubble trap in the external circuit. It and the Sigmamotor pump are opened and blood is allowed to fill the external circuit, the lung being excluded. Blood is then circulated with the trap closed until no more air bubbles collect.

The lung circuit is best primed just before it is needed, after the priming of the external circuit. When the lung is below the level of the pumps, initial filling is best accomplished by gravity. As soon as blood appears at the lung outlet, the venous pump is started (the arterial pump is not run at this time) and run until no further bubbles collect in the bubble trap and until the outlet pressure has been properly regulated. If it appears advisable to run gas

through the lung during the priming because of slight leakage, it may be best to use air to prevent hyperoxygenation and then to shift to oxygen at the start of the perfusion. One liter of gas per meter of membrane provides adequate flow.

V. *Operation.*—

If the venous pressure reservoir is placed at the level of the animal's or patient's venous pressure, no control clamps are required on the lines and the heart lung may be started or stopped by simply turning it on or off. The venous pressure can then be kept at a normal level by lowering the reservoir as required.

If the apparatus is properly set up with a flow of about 100 c.c. per meter of membrane, the inlet pressure will vary between approximately 75 and 150 mm. Hg. There appears to be no advantage in monitoring this pressure. As mentioned above, the outlet pressure is important. For safety, in case of leakage to prevent gas embolization, it should be kept above the maximum pressure which can be attained in the gas phase. Filming, also, appears to be somewhat more even if a positive pressure is kept at the outlet (see Priming).

A shunt is provided between the arterial and the venous lines which serves to balance the flow of the two pumps. This prevents any pressure differential and makes it unnecessary to have the pumps exactly the same. Hyperoxygenation may be prevented by running the venous pump at a slightly slower rate than the arterial pump. This will cause the arterial pump to take up a small amount of venous blood which will then absorb the excess dissolved oxygen. If some re-circulation through the lung is desired, this is readily provided by running the venous pump at a rate faster than the arterial pump. Regulation can be done visually by observing the color of the blood.

Small leaks are not infrequent and large leaks may occur occasionally if there is a tear in the membrane or if the lung is put together incorrectly. For clinical use, therefore, we recommend that the lung be tested before sterilization (see Assembly). A small leak in no way interferes with proper function and even large leaks are dangerous primarily because of blood loss through them.

In the laboratory we have utilized 4 mg. per kilogram of heparin in addition to 15 to 20 mg. for each 500 c.c. of priming blood. In the human being, we have used only 2 to 3 mg. per kilogram. There does not appear to be any danger in using extra heparin as it is readily neutralized later. There is, however, a danger in using too little heparin as there may be fibrin deposition in portions of the apparatus where the flow is not perfectly streamlined. This is very slight in the lung itself.

VI. *Monitoring.*—

As mentioned before, the membrane lung makes it possible to reduce monitoring to a minimum. The function of the apparatus is predictable and this eliminates the necessity of following oxygenation, pH, arterial pressure, and many other things which are generally watched carefully. In the final analysis everything can be pre-set except the venous pressure. We believe that this should be followed and regulated.

VII. *Re-use of Membrane and Tubing.—*

This has been tried with unsatisfactory results and is not recommended. If the lung is not disassembled, it is impossible to clean it adequately. If it is taken apart, it is almost impossible to avoid tearing the membrane where it has been made adherent by the use of the cautery. In the animal laboratory we have repeatedly re-used the tubing, venous reservoir, and bubble traps, without any apparent difficulty. The circuit is, however, carefully taken apart and all joints cleaned and re-assembled. In the human being, we have preferred to re-use only the special nylon joints and the blood distribution discs. Everything else in the circuit is readily disposable and relatively inexpensive.

SUMMARY

The Teflon membrane lung is the nearest approach to an ideal lung substitute that is presently available. Although it is not so good as the biologic lung, it performs equally as well for the limited demands of intracardiac surgery. When one considers the relative time required for the development of each of these lungs, this is remarkable.

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ANAPHYLACTOID SHOCK DUE TO HOMOLOGOUS BLOOD EXCHANGE IN THE DOG

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DURING the experimental development of techniques for cardiopulmonary bypass, shock-like states were frequently encountered when dogs were perfused without change in blood volume. Further studies were undertaken to determine the mechanism of these reactions.

METHODS

Five different techniques for blood exchange were used: (1) total cardiopulmonary bypass, (2) transfusion, (3) veno-arterial pumping, (4) left heart bypass, and (5) blood exchange with constant volume.

During 75 total cardiopulmonary bypass experiments in dogs shock was often masked by volume changes. The blood volume of the recipient is necessarily increased by transfusion, so this technique was not extensively studied. In the remaining three methods, extensive blood exchange was produced with closed extracorporeal circuits of fixed volume so that no change in the blood volume of the animal was possible. Veno-arterial pumping consists of the transfer of the superior caval return to the lower aorta without oxygenation,[1] and left heart bypass involves pumping oxygenated blood from the left atrium to the aorta. Blood exchange with constant volume was performed by placing 200 ml. of blood from each donor animal in a closed flask suspended above the recipient and connected to cannulae in the femoral artery and vein. On opening the cannulae, pressure in the flask rose 25 to 30 mm. Hg and blood exchange occurred, the volume of blood in the flask increasing by less than 50 ml.

Mongrel dogs weighing 15 to 25 Kg. were used throughout. Donor blood was obtained from animals lightly anesthetized with 250 to 350 mg. of Pentothal sodium by bleeding from a femoral artery into bottles containing 30 mg. heparin per liter of blood. Subject dogs were similarly anesthetized and secured supine on the operating table. Normal respiration was allowed unless thoracotomy was part of the procedure when artificial ventilation was maintained through an endotracheal tube.

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Arterial pressure was monitored by means of a polyethylene catheter placed in the aortic arch through the femoral artery, and systemic venous pressure by a similar catheter passed into the inferior vena cava via a femoral vein. Portal venous pressure was recorded in some experiments using a catheter inserted through a small abdominal incision into the cranial mesenteric vein. Pressures were recorded with Statham P23D strain gauges and a Cambridge direct-writing recorder.

The extracorporeal circuit for cardiopulmonary bypass consisted of a venous reservoir, a Gibbon-type oxygenator, and rotary pumps. The priming volume of this circuit was about 3,000 ml. and blood from 4 or 5 donors was usually required. The circuits for veno-arterial pumping and for left heart bypass were of 800 ml. capacity and were usually filled with blood from 1 donor, although occasionally 2 donors were needed. In the experiments with simple blood exchange, from 1 to 4 donors were used. With all techniques, blood exchange was begun at between 300 and 600 ml. per minute. Various courses were followed subsequently. When shock was evident, exchange was sometimes stopped so that the hemodynamic changes could be observed without disturbance; in other studies extracorporeal flow was maintained.

The effects of intravenous injection of *Escherichia coli* endotoxin in doses from 1 to 7 mg. were observed in similar preparations.

RESULTS

The incidence of shock was similar with each of the techniques for blood exchange without change in volume (Table I).

TABLE I. INCIDENCE OF SHOCK FOLLOWING BLOOD EXCHANGE

EXPERIMENTAL PROCEDURE	NUMBER OF EXPERIMENTS	INCIDENCE OF SHOCK
Veno-arterial pumping	55	17
Left heart bypass	8	3
Constant volume blood exchange	47	21
Totals	110	41

Simple transfusion with 200 ml. of homologous donor blood caused shock in 3 out of 6 trials. Exchange using autogenous blood produced no effect, although in 10 of the 16 trials the blood was deliberately poorly heparinized and contaminated. The incidence of shock increased considerably when blood from more than 1 donor was used to fill the extracorporeal circuit (Table II). In total cardiopulmonary bypass, where blood from 4 or more animals was used to prime the system, evidence of shock appeared as arterial hypotension, reduced venous return or blood transfer from extracorporeal circuit to subject animal in all cases in which adequate data were available for analysis.

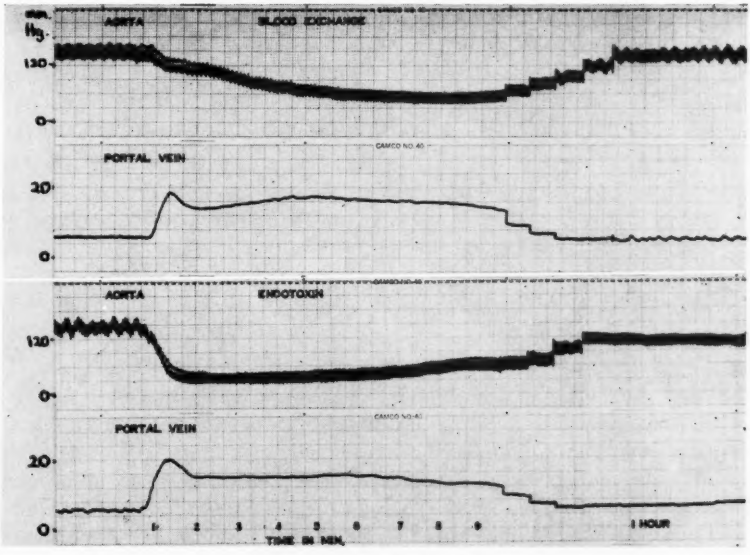
An abnormal reaction to blood exchange was usually apparent in 1 minute as a sharp rise of portal venous pressure associated with distention of the liver and the portal venous radicals. The subsequent course was similar whether blood exchange was discontinued or maintained, providing the volume of blood

TABLE II. RELATION BETWEEN NUMBER OF DONORS AND INCIDENCE OF SHOCK
(114 EXPERIMENTS WITH EXTRACORPOREAL CIRCUITS OF FIXED VOLUME)

NUMBER OF DONORS	NUMBER OF EXPERIMENTS	INCIDENCE OF SHOCK
1	86	25
2 or more	28	17

in the animal and in the extracorporeal circuit remained constant. The systemic venous pressure was unchanged but the venous return diminished rapidly and there was a corresponding fall in arterial pressure. Maximal pressure changes were attained in 3 to 5 minutes, the portal venous pressure reaching 40 mm. Hg in the more severe cases and the mean arterial pressure falling to 20 mm. Hg (Fig. 1, *A*). Slight degrees of shock, on the other hand, produced a rise of portal venous pressure of only 1 or 2 mm. Hg, the small fall in arterial pressure being difficult to recognize. During the next hour the pressures returned almost to normal levels, although portal distention was still apparent.

A.



B.

Fig. 1.—*A*, Effect of homologous blood exchange on the arterial and portal venous pressure with an extracorporeal circuit of fixed volume.
B, Similar changes in arterial and portal venous pressure following the injection of *Esch. coli* endotoxin.

If bypass was continued and the volume of the extracorporeal circuit kept constant, the reduction in venous return necessarily limited the extracorporeal flow. In the less severe degrees of shock, the venous return and arterial pressure could be maintained by allowing the animal to take up blood from the extracorporeal circuit (Fig. 2). Perfusion could then be continued at acceptable extracorporeal flow rates, but only at the expense of further distention of

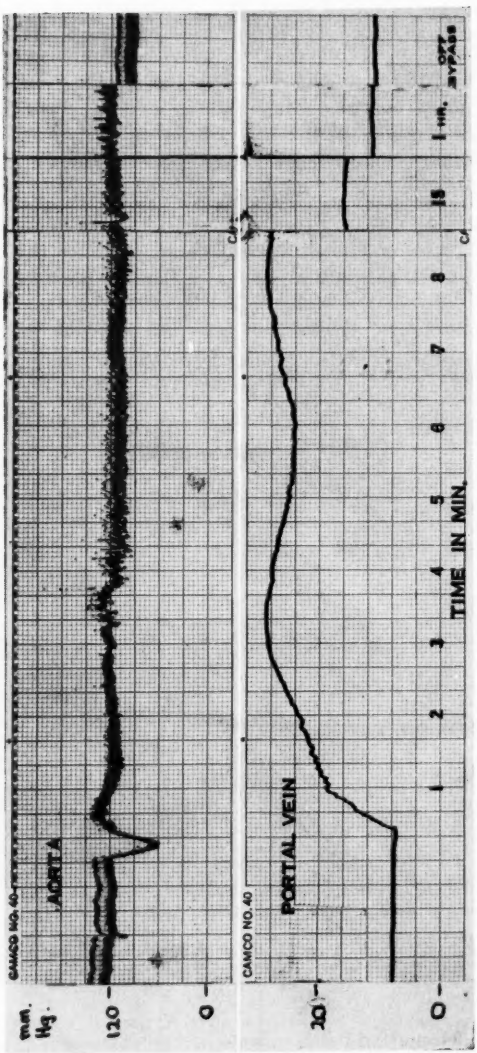


Fig. 2.—Effect of homologous blood exchange on the arterial and portal venous pressure in total cardiopulmonary bypass. The animal was allowed to take up blood from the extracorporeal circuit from the onset of blood exchange.

the portal system. Some animals tended to recover control of their vascular volume toward the end of a 1-hour period of perfusion and returned some blood to the extracorporeal circuit. More often, however, there was a serious fall in blood pressure at the termination of bypass, the excess blood was retained and the animals failed to recover consciousness.

In an attempt to localize the agent in blood responsible for the shock reaction, two experiments were performed in which the donor cells and plasma were separated by centrifuging. Blood exchange with donor cells suspended in saline produced no ill effect, but shock resulted from exchange using the plasma from these animals.

Injections of *Esch. coli* endotoxin, in varying dosage, produced hepatic engorgement and changes in the portal venous and systemic arterial pressures similar in degree and timing to those resulting from blood exchange (Fig. 1, *B*).

DISCUSSION

A number of studies of blood transfusion in normal dogs have shown that added plasma is rapidly lost from the circulation.[2-5] In one of these studies, 6 out of 34 dogs showed urticaria and a fall in blood pressure.[3] Other reports of the effects of plasma transfusion in dogs indicate that urticaria is almost invariable.[6, 7] Similar reactions were found during experimental hemodialysis by the Mayo Clinic group.[8, 9] A fall in blood pressure with bradycardia, respiratory depression, and urticaria was noted at the onset of hemodialysis in 27 of 37 dogs and was associated with a mortality of more than 30 per cent. These reactions were eliminated by priming the extracorporeal circuit with autogenous blood, saline solution, or some dextrans. More severe changes of this type have been found following plasma infusion in the adrenalectomized dog.[10, 11] Urticaria is generally much less prominent in experiments performed under anesthesia.[7, 11]

It has been shown that plasma reactions are not related to the blood group of the dogs or the presence of plasma iso-agglutinins.[7, 8] Natural isoantibodies are found in only about 15 per cent of random dogs, and are mostly of low potency.[12, 13] The suggestion that incipient coagulation due to suboptimal heparinization of blood is responsible for these changes after transfusion[14] is not supported in our present studies, as poorly heparinized autogenous blood did not produce shock.

When reactions to plasma transfusion were first noticed, their similarity to histamine effect[7, 11] and to anaphylactic shock[6] was remarked. Anaphylaxis in the dog is associated with an acute fall in blood pressure and elevation of portal venous pressure with segregation of blood in the portal venous system and liver.[15, 16] The mechanism has been a subject for considerable discussion[17-19] but it seems likely that diffuse spasm of the smooth muscle in the hepatic venous system is mainly responsible.[20] There is good evidence that anaphylactic shock is due to histamine release.[21-24]

Anaphylactoid shock, that is, a syndrome resembling anaphylaxis but not associated with demonstrable previous sensitization, has been found frequently

in response to the injection of a wide variety of substances.[25, 26] These include colloidal iron, peptone, rattlesnake venom,[27] hydatid fluid,[28] and Ascaris extracts.[29] The endotoxin produced by gram-negative bacteria has a similar effect and has been investigated in detail.[26, 30, 31]

The similarity of the changes described here with homologous blood exchange to those described in anaphylaxis in dogs is apparent, and we have been able to reproduce most of the effects by the injection of *Esch. coli* endotoxin. It seems, therefore, that there is an agent in dog blood which produces anaphylactoid shock. The effect is evident in less than one third of donors, but, when mixed blood from many donor animals is used, the incidence of shock is considerably greater. Our fractionation studies suggest that a plasma factor is responsible, although other workers have reported reactions to washed red cells.[6, 7]

The resemblance of the effects of gram-negative bacterial endotoxins to the changes that follow blood exchange has lead to the suggestion that endotoxin is present in donor blood as a result of bacteremia when the animal is exsanguinated. However, reactions were no less frequent in experiments in which only 200 ml. of blood was taken from each donor.

It has been suggested[32] that reactions of this type occurring during the course of cardiopulmonary bypass were due to acidosis. Similar changes have been produced by CO_2 retention or hydrochloric acid infusion. The shock-like effects reported here, however, were evident at the onset of blood exchange before acidosis had occurred. This does not exclude the possibility that acidosis itself may produce shock.

Anaphylactoid responses to blood exchange may interfere considerably with the interpretation of physiologic studies in dogs. Conclusions based on experiments involving blood exchange in which this factor is not recognized must be interpreted with caution. The more severe varieties of anaphylactoid shock will be detected easily by observation of the arterial pressure during the first few minutes of blood exchange, providing the volume of blood in the extracorporeal circuit is kept constant. However, minor variants may be missed unless the portal venous pressure is measured. In cardiopulmonary bypass, detection of these effects is especially difficult as venous return and perfusion can be maintained if the animal is allowed to take up blood from the extracorporeal circuit.

A preliminary test transfer of 200 ml. of donor blood can be used to determine whether an anaphylactoid reaction will occur. If shock is produced, an interval of 1 hour will allow the arterial and portal venous pressures to return to normal. Useful experimental data can then be obtained, but many of the effects of shock on the circulation and the liver probably persist.

It has been reported that antihistamines[7, 11] or adrenergic blockade[8, 9] will reduce the effect of plasma infusion, and large doses of hydrocortisone have been shown to prevent endotoxin shock.[33] These findings suggest that animals can be protected against reactions to blood exchange, but the large doses of potent agents required may produce other undesirable effects.

SUMMARY AND CONCLUSIONS

1. Blood from about a third of donor dogs produced a shock-like effect in the recipient animal. The incidence is greater when mixed blood from a number of donors is used.

2. The onset of shock is characterized by a rapid rise in portal venous pressure with distention of the liver and portal system.

3. If the volume of the extracorporeal circuit is fixed, the arterial pressure falls as the portal venous pressure rises, suggesting that sequestration of blood is occurring in the portal system. The venous return and, consequently, the extracorporeal flow are reduced in these circumstances.

4. The portal venous and arterial pressures tend to recover in the course of an hour but the portal congestion persists.

5. If the animal is allowed to take up blood from the extracorporeal circuit, the arterial pressure and venous return are better maintained, but sequestration in the portal system is accentuated.

6. The syndrome is similar to the effects of anaphylaxis in the dog.

7. Reactions of this type following blood exchange may interfere with the interpretation of experimental studies in dogs.

8. A preliminary test exchange with 200 ml. of donor blood can be used to determine whether shock will occur in any particular experiment.

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THE EFFECTS OF ANAPHYLACTOID SHOCK FROM BLOOD EXCHANGE ON CARDIOPULMONARY BYPASS IN THE DOG

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INTRODUCTION

During 75 cardiopulmonary bypass experiments in dogs it became apparent that there was a tendency for the animals to take up blood from the extracorporeal circuit. A study of the effects of homologous blood exchange in dogs[1, 2] demonstrated that blood from approximately one third of random donors produced a state resembling anaphylactic shock, with sequestration of blood in the liver and portal venous system. The present study was undertaken to assess the effects of anaphylactoid shock resulting from blood exchange on the course of cardiopulmonary bypass in the dog.

METHODS

Mongrel dogs weighing 15 to 25 Kg. were used throughout. Donor blood was obtained from animals lightly anesthetized with Pentothal (15 mg. per kilogram body weight), by arterial exsanguination into bottles containing 30 mg. of heparin per liter of blood. Subject dogs were anesthetized with Nembutal (25 mg. per kilogram body weight) and secured supine on the operating table. Aortic blood pressure was monitored by a polyethylene catheter in the femoral artery, and portal venous pressure by a catheter placed in the cranial mesenteric vein through a small abdominal incision.

The effects of blood exchange were investigated using a simple extracorporeal system in which 200 ml. of blood from each donor was suspended in a liter flask above the animal and connected to cannulae in a femoral artery and vein. When the cannulae were opened, pressure in the flask rose 25 to 30 mm. Hg and blood exchange occurred, the volume of blood in the flask increasing by less than 50 ml. Blood samplers were obtained when the shock was maximal (3 to 5 minutes). Blood exchange was then discontinued and further samples taken after an hour.

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Cardiopulmonary bypass was performed with a venous reservoir, a rotating disc oxygenator, and a pump with ball valves at each end of a silicone rubber chamber driven by pulses of compressed air.[3] Cannulation was performed without opening the thorax. The venous cannulae were inserted through a femoral vein into the inferior vena cava and through the right external jugular vein to the superior vena cava. The arterial cannula was placed in a femoral artery. Side arms on each venous cannula enabled blood samples to be obtained, and mixed venous and arterial samples were available from the inflow and outflow lines of the oxygenator. When total bypass was performed, an endotracheal tube was inserted and ventilation maintained with a respirator. The right chest was then opened and ligatures placed around the venae cavae proximal to the cannulae. The coronary venous return was allowed to pass through the heart normally. Cardiopulmonary bypass was maintained for 60 minutes in each animal and blood samples were obtained at 20-minute intervals. Extracorporeal flow was measured by determining the time taken for the volume of the venous reservoir to increase 100 ml. when its outflow line was temporarily occluded.

Pressures were measured with Statham P23D strain gauges and a Cambridge direct writing instrument. Blood oxygen and CO_2 contents were measured,[4] as were the plasma pH, hematocrit, electrolytes, lactate,[5] and pyruvate.[6] The oxygen saturation was expressed as a percentage of the hemoglobin capacity without correction for the oxygen in solution. A nomogram[7] was used to derive the pCO_2 and buffer base.

RESULTS

Twenty-two animals were studied and five different types of experiments were performed (Table I). Shock was evident in all bypass studies, and blood exchange experiments that did not show shock were excluded.

TABLE I

A. Blood exchange alone	(4 animals)
B. Blood exchange followed after 1 hour by total bypass without change in blood volume	(4 animals)
C. Total bypass without change in blood volume	(5 animals)
D. Total bypass with hypervolemia	(5 animals)
E. Partial bypass with hypervolemia	(4 animals)

In all experiments the blood pressure fell sharply, sometimes to less than 50 mm. Hg, and the portal venous pressure increased (average rise from 7 to 22 mm. Hg), the liver and portal venous radicals becoming distended. These changes began approximately 1 minute after the onset of blood exchange and were maximal in 3 to 5 minutes.

In Groups A, B, and C (13 animals) the effects of shock were studied. Apnea occurred during the period of shock in some animals and the arterial oxygen saturation fell correspondingly. There was a profound fall in venous oxygen saturation during shock, the arteriovenous oxygen difference reaching nearly double the control value. The hematocrit tended to rise as soon as shock was apparent and this increase was greater after 1 hour. Buffer base fell nearly 3 mEq./L. on the average and there was a rise of approximately 1 mEq./L. in the blood lactate. The sodium and chloride levels boths rose about 1.5 mEq./L., but there was no significant change in the plasma potassium (Table II).

TABLE II. EFFECTS OF ANAPHYLACTOID SHOCK FROM BLOOD EXCHANGE (13 ANIMALS) AND OF CARDIOPULMONARY BYPASS (18 ANIMALS)

	MEAN CONTROL VALVES	SHOCK	RECOVERY	BYPASS		
Time (min.) from onset of blood exchange		3 to 5	60	20	40	60
Hematocrit (%)	51	+1.3	+2.6	+1.7	+2.8	+1.6
Buffer base (mEq./L.)	45	−2.9	−2.4	−3.4	−6.0	−7.3
Na + (mEq./L.)	154	+0.8	+1.6	−2.2	−2.6	−0.4
Cl − (mEq./L.)	109	+1.8	+1.4	−0.1	+2.1	+2.6
K + (mEq./L.)	4.3	+0.1	−0.3	−0.4	−0.7	−0.6
Lactate (mEq./L.)	2.1	+1.7	+0.8	+1.5	+2.1	+2.7
Pyruvate (mEq./L.)	0.15	+0.1	+0.05	+0.05	+0.1	+0.1

The changes resulting from blood exchange associated with bypass were studied in Groups B, C, D, and E (18 animals). Those perfused without change in blood volume showed a fall in flow and arterial pressure at the onset of blood exchange, but when the animal was allowed to take up blood from the extracorporeal circuit the fall in arterial pressure was less and satisfactory venous return and bypass flow were maintained. The volume change ranged from 400 to 1,400 ml. The optimal bypass flow in each animal was between 0.5 and 1.6 L./min./M.^{2} (mean 1.0 L./min./M.^{2}). The arterial oxygen saturation was well maintained but there was a considerable increase in the arteriovenous oxygen difference, both in partial and total bypass experiments. The hematocrit rose by approximately the same amount as in shock. A metabolic acidosis developed during bypass, the buffer base falling by 7 mEq./L. and the blood lactate rising by 2.5 mEq./L. over a period of an hour. The pyruvate changes were similar to the lactate but on a much smaller scale. The sodium levels fell by 2 mEq./L. at 20 and 40 min., returning to normal at 60 min. Chloride levels rose by 2 mEq./L. at 40 and 60 min. There was a fall of about 0.5 mEq./L. in the plasma potassium during the period of bypass (Table II).

In two additional partial bypass studies, the effects of blood exchange were modified. In 1 animal, a side-to-side anastomosis was made between the portal vein and the inferior vena cava before bypass was begun. There was no rise in portal venous pressure or fall in arterial pressure on blood exchange and

the venous oxygen contents were unchanged, although the liver became considerably distended. In the second animal, 400 mg. of diphenhydramine was given. The portal venous pressure rose at the onset of bypass but there was no fall in arterial pressure or venous oxygen content.

The metabolic effects were similar in both these animals (Table III). The hematocrit fell slightly as did the buffer base. The lactate rose 2 mEq./L., the pyruvate 0.2 mEq./L., after an hour. The electrolyte changes were similar to those found in the other experiments, the sodium falling 3 mEq./L., the potassium 0.5 mEq./L., and the chloride rising 3 mEq./L.

TABLE III. EFFECTS OF BYPASS IN 2 ANIMALS WITH MODIFIED RESPONSE TO BLOOD EXCHANGE

	MEAN CONTROL VALUES	BYPASS		
Time (min.) from onset of blood exchange		20	40	60
Hematocrit (%)	51	−0.3	−0.7	−1.3
Buffer base (mEq./L.)	44	0	−0.2	−0.8
Na + (mEq./L.)	154	−1.0	−3.0	−3.0
Cl − (mEq./L.)	114	0	+1.5	+3.0
K + (mEq./L.)	3.3	−0.1	−0.6	−0.5
Lactate (mEq./L.)	2.3	+1.7	+1.0	+2.0
Pyruvate (mEq./L.)	0.1	+0.15	+0.15	+0.2

A further experiment was performed in which the extracorporeal circuit was filled with gelatin solution. There was no fall in arterial pressure or elevation of portal venous pressure following bypass in this animal.

DISCUSSION

Unusual responses to transfusion of various blood components have been found in dogs,[8-17] and shock-like changes have been reported by many workers with the extracorporeal circulation. The release of toxin from cellophane,[18] incipient coagulation due to suboptimal heparinization,[19] and the absence of pulsatile flow[20] have been suggested as possible mechanisms but seem unlikely in view of subsequent work.[1, 2, 14, 21] Experimental studies[1, 2] indicate that anaphylactoid shock is produced by 200 ml. of plasma from approximately one third random canine donors. In total cardiopulmonary bypass, where the extracorporeal circuit has a large volume, blood from 3 or more donors is needed to fill the circuit. In these circumstances there was evidence of shock in all our procedures for which adequate data were available. No shock occurred when the circuit was primed with gelatin, and the response was considerably modified by preliminary portocaval anastomosis and by diphenhydramine.

Anaphylactoid shock from blood exchange has a considerable effect on the course of cardiopulmonary bypass in the dog. Sequestration of blood in the liver and portal venous system leads to a reduction in venous return, and so restricts the extracorporeal flow. Systemic perfusion is reduced and the blood

pressure falls. If the animal is allowed to take up blood from the extracorporeal circuit, the venous return and blood pressure may be maintained, but at the expense of a further increase in hepatic and portal venous congestion.

Metabolic acidosis during cardiopulmonary bypass is, at least in part, the result of accumulation of acid metabolites due to incomplete oxygenation. In the present study the increase in blood lactate accounts for about a third of the fall in buffer base. There is also an increase in blood pyruvate but the changes are trivial. However, it is probable that lactate is only a small and variable fraction of the total organic acid accumulation.[21]

A similar acidosis occurs as a result of anaphylactoid shock from blood exchange which is an integral part of the response to bypass in the dog. Both in isolated shock and in bypass, direct measurement and the changes in arteriovenous oxygen difference indicate that systemic blood flow falls considerably. Decreased tissue perfusion may be responsible for the acidosis. The absence of metabolic acidosis during veno-arterial pumping,[23] in which the lower part of the body is perfused with unsaturated blood and total systemic blood flow is unchanged, suggests that tissue hypoxia is not the causative factor.

The hepatic congestion produced by the anaphylactoid response to blood exchange is present during bypass and may be a factor in the production of acidosis. Even when an interval of 1 hour was allowed after blood exchange, considerable portal congestion persisted. Anaphylactoid shock from blood exchange is associated with a rise in hematocrit and plasma electrolyte levels which suggests hemoconcentration and loss of water to the cells. During cardiopulmonary bypass there is a fall in plasma sodium and potassium and a rise in chloride indicating a major electrolyte shift tending to produce acidosis. Similar changes were noted by Pontius and his associates.[24]

In the two bypass experiments in which the anaphylactoid response was modified, systemic perfusion was maintained near normal levels. Although the electrolyte changes and accumulation of organic acids were similar to those found in other bypass studies, there was little impairment of buffer base, suggesting that shock from blood exchange or inadequate systemic perfusion may produce metabolic acidosis in other ways.

The relation of anaphylactoid shock in dogs to hypotension or acidosis in human extracorporeal circulation is problematical. Hemodialysis studies at the Mayo Clinic suggests that similar reactions may occur in a number of human cases of massive blood exchange.[13] There is evidence that a vasoconstrictor mechanism exists in the hepatic veins of man,[25] so that similar reactions to those described here in dogs may be of importance in human work.

SUMMARY AND CONCLUSIONS

1. Blood from about one third of donor dogs produces anaphylactoid shock in the recipient animal.

2. Anaphylactoid shock is an integral part of the response of the dog to cardiopulmonary bypass as a large volume of blood from many donors is used to fill the extracorporeal circuit.

3. Anaphylactoid shock in the dog is associated with sequestration of blood in the liver and portal venous system. Bypass flow and arterial pressure fall, but the changes are less evident if the animal is allowed to take up blood from the extracorporeal circuit.

4. Accumulation of organic acids was found in anaphylactoid shock, either occurring alone or in association with cardiopulmonary bypass. Systemic perfusion was below normal levels in both situations. Cardiopulmonary bypass was also associated with an electrolyte shift producing metabolic acidosis.

5. Modification of the anaphylactoid response by a portocaval anastomosis, or by diphenhydramine, allowed bypass without a reduction of systemic blood flow. Although there was organic acid accumulation and similar electrolyte changes to those found in other bypass studies, there was little metabolic acidosis in these experiments.

6. Responses to massive blood exchange similar to those described here may be of importance in human work.

The initial 75 cardiopulmonary bypass studies were performed in the Boston University Surgical Research Laboratory at the Boston City Hospital, Boston, Mass., through the courtesy of Dr. John J. Byrne. Our thanks are due to Miss Jessica Nolan for the biochemical work and to Miss Esther Chang for help with the bibliography.

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VENO-ARTERIAL PUMPING IN NORMAL DOGS AND DOGS WITH CORONARY OCCLUSION

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PARTIAL BYPASS of the heart appears to be a reasonable approach to the problems of coronary shock and intractable heart failure. If partial perfusion of the body can be instituted safely for prolonged periods, the decreased work required of the heart may allow an infarcted or failing heart to maintain adequate coronary flow and subsequently to recover.

Stuckey and his co-workers[1] reported their experience in the use of a heart-lung machine in patients with severe myocardial infarction. We wondered whether a pump without an oxygenator would be of clinical value in similar patients. We theorized that a pump alone might relieve the heart of some of its work, help maintain or improve coronary flow, and be available for emergency use at very short notice. It was hoped that the reduced cardiac output through the lungs would be sufficient to accomplish satisfactory oxygenation of blood going to the heart, brain, and kidneys and that the lower part of the body would withstand the relative anoxia. Hamer and his associates[2, 3, 4] have recently reported their results with arterial perfusion of venous blood. They proposed its use in patients with heart failure and myocardial infarction. We felt that our experimental data, however meager, should be made immediately available in order to emphasize the potential dangers of veno-arterial pumping in patients with myocardial infarction.

MATERIALS AND METHODS

Jugular vein blood was pumped into a femoral artery with a Sigmamotor pump in 14 dogs. The perfusion circuit generally established is shown in Fig. 1. Whenever the venous blood was pumped into the brachial or carotid artery instead of the femoral artery, the animal responded poorly, due to the perfusion of the heart and brain with poorly oxygenated blood.

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Sampling catheters were placed in the aorta at the level of the diaphragm and in the aortic arch. This was accomplished via the femoral and carotid arteries, respectively. The blood pressure was monitored with a mercury manometer by means of a cannula in the brachial artery. The perfusion rate was obtained by measuring the decrease in blood volume within the graduated collecting reservoir over a 15-second period with the inflow tubing occluded. An alternative method was to divert the venous drainage into a graduated cylinder for a 15-second period. The two methods checked closely.

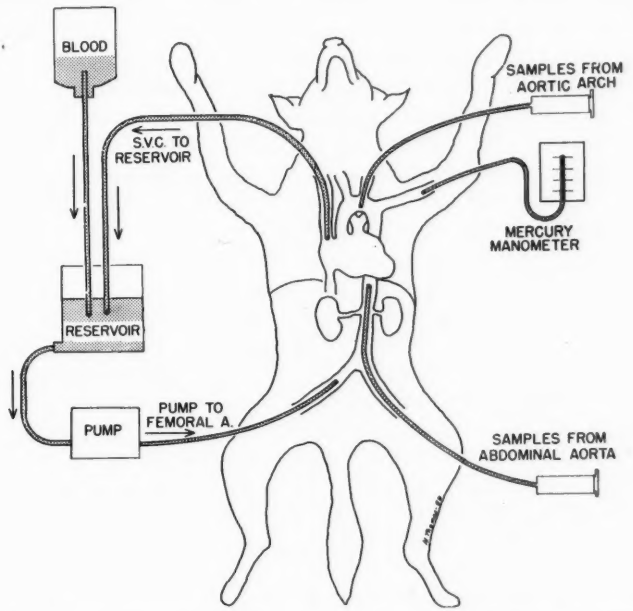

Fig. 1.—Diagram showing perfusion circuit and location of sampling catheters.

Most of the animals were anesthetized with intravenous Nembutal and the trachea was intubated. This permitted ventilation with a 95 per cent oxygen-5 per cent carbon dioxide mixture through an Emerson intermittent positive pressure respirator. While on this mixture, the blood carbon dioxide usually remained within normal limits. Although a few animals were perfused under morphine and local anesthesia, having the animal quieter under barbiturate was a great advantage and therefore was preferred.

Most of the experiments were not conducted with sterile precautions and the animal was later sacrificed. Heparinization was accomplished with a dose of 1 mg. per pound. The rate of perfusion was determined by the maximum rate of venous flow that could be obtained under different experimental conditions.

In order to produce coronary artery occlusion, a No. 1 silk ligature was loosely looped about the anterior descending branch of the left coronary artery

(LAD) with a surgeon's knot and the ends of the ligature were buried subcutaneously several weeks in advance. When occlusion was required, the two ends of the suture were exposed and pulled taut. The effectiveness of the acute coronary occlusion was checked by electrocardiographic tracings and later postmortem examination.

RESULTS

In 10 normal dogs, 15 to 25 kilograms, veno-arterial pumping with unoxygenated blood was performed for periods varying from 3 to 5 hours at rates varying from 300 to 1,000 ml. per minute. Once the technical problems of pumping were mastered, survival of the animal could be expected. Our oxygen saturation studies indicated that the venous blood pumped into the femoral artery did not lower the oxygen saturation of the blood above the level of the renal arteries. This held true only as long as the animal's blood pressure was maintained within normal limits. Long-term survival was observed in the only dog pumped under sterile precautions. Experiments on the other 9 dogs were terminated at the end of the perfusion period.

In 4 dogs, coronary artery occlusion was produced prior to starting the pump. In each instance the blood pressure was satisfactory for 30 minutes until the pumping with venous blood began. Within 10 minutes thereafter, the blood pressure fell precipitously in all 4 instances. Cyanosis of the mucous membranes of the head was observed. Blood pressure was temporarily restored by blood transfusion and norepinephrine, in 2 of the 4 animals. Maximum flow rates of 100 to 600 ml. per minute were obtained. Death occurred at 8, 10, 15, and 60 minutes after instituting pumping. Electrocardiographic examination and postmortem examination indicated that 2 of these animals had had an acute coronary artery occlusion produced by the previously placed ligature. The other 2 dogs had older occlusions, apparently produced sometime following the placement of the ligature several weeks previously. Their performance on veno-arterial pumping was no better than the 2 dogs with fresh occlusions, 1 of which survived for 60 minutes.

DISCUSSION

The results obtained suggest that a partial bypass with unoxygenated blood may be tolerated by a dog with a normal heart. A line of demarcation between oxygenated and unoxygenated blood can be obtained near the level of the diaphragm. This point was also demonstrated by Hamer and his co-workers[2] who used a radiographic technique. However, when a fresh or recent coronary artery occlusion exists, the dogs do not tolerate veno-arterial pumping. Presumably, the myocardium no longer has the ability to maintain a satisfactory cardiac output against the action of the pump. Venous blood perfuses the upper arterial tree and rapid deterioration in the condition of the animal ensues. Dogs which had satisfactorily compensated for a coronary artery occlusion were promptly thrown into irreversible shock when venous blood was pumped into their arterial systems via the femoral artery.

We have had no experience with animals in heart failure. Theoretically, veno-arterial pumping might be of benefit in patients with right heart failure.[5] The failing right ventricle would be relieved by continuous phlebotomy while the pump returned the blood to the arterial side. This would increase the load on the left ventricle but also would increase the coronary artery perfusion. However, the newer heart-lung machines are being improved in simplicity and efficiency to the point where there seems to be little advantage or justification for using the pump alone.

SUMMARY

Venous blood was pumped into the femoral artery of 10 normal dogs for 3 to 5 hours without serious adverse effect. When fresh or recent coronary artery occlusion was produced in 4 additional dogs, the same procedure produced irreversible shock within 10 minutes. It is concluded that veno-arterial pumping in patients with coronary artery occlusion would be harmful rather than beneficial.

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POTASSIUM ION AS A CARDIOPLEGIC AGENT IN TOTAL CARDIAC BYPASS AND DURING HYPOTHERMIA WITH CORONARY PERFUSION

An Experimental Study

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THE REVERSIBILITY of potassium induced cardioplegia does not follow a systematic pattern. Its unpredictability places it in the category of methods requiring discriminative and judicious application. Because of the limited physiologic knowledge available, we have attempted to elucidate information concerning the fate of this ion when used in cardioplegia. In a previous report[5] from this laboratory, it was noted in normothermic and hypothermic animals that (a) the reversibility of cardioplegia was not uniformly related to the amount of potassium injected or to its concentration in the myocardium, (b) "washing out" potassium was not synonymous with resumption of normal rhythm, and (c) hypothermic animals subjected to such arrest suffered much greater mortality than was observed in a comparable group of normothermic dogs. Prior digitalization of the former group, however, had a beneficial effect.

In a continuation of these studies, the metabolism of potassium during cardioplegia has been observed in dogs subjected to total cardiac bypass and in hypothermic animals with venous inflow occlusion and coronary perfusion. The purpose of this paper is to present information obtained concerning the fate of this ion under these circumstances.

METHOD

Thirty-two mongrel dogs of both sexes, weighing 15 to 25 Kg., were equally divided into two groups—Group I comprised those having total cardiac bypass, and Group II those having hypothermia with coronary perfusion. All animals were anesthetized with intravenous thiopental, 35 mg. per kilogram, and supplemented with ether when additional anesthetic was required.

A bubble oxygenator and Sigmamotor pump were employed for the achievement of total cardiac bypass in Group I animals. Body temperature was continuously monitored and maintained at normothermic levels. The extracorporeal

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system was primed with heparinized blood (18 mg. of heparin per 500 ml.) which had been collected in siliconized bottles from healthy dogs the day of the experiment. Following insertion of two Tygon catheters (3/8 inch internal diameter) into the venae cavae through the right auricular appendage and through a purse-string suture in the wall of the right atrium, they were joined to a Y tube and venous blood was collected by gravity into a reservoir, 50 cm. below the level of the right atrium. The arterial line was connected to a No. 16 plastic catheter which was inserted into either the femoral or the subclavian artery. Pump flow averaged 65 ml. per kilogram per minute.

Animals in Group II were made hypothermic by surface cooling in a fashion precisely as described many times previously from this laboratory.[3-5] They were maintained at a body temperature of 28° to 29° C. during the experiment. Artificial respiration was carried out by means of an automatic respirator. Coronary perfusion during the period of venous inflow occlusion was accomplished by connecting a reservoir of heparinized blood maintained at 37° C. to a No. 16 plastic catheter which was inserted via the subclavian artery into the ascending aorta. Constant flow (avg. 100 ml./min.) and pressure (130 mm. Hg) of the perfusate were maintained.

During venous inflow occlusion, coronary sinus blood was withdrawn from the right atrium in Group I by needle puncture, and in Group II by a catheter inserted into the atrium through the jugular vein. This served to prevent distention of the right heart as the result of the coronary perfusion, to permit blood sampling for quantitative study, and to remove the potassium solution used to induce standstill which, after traversing the coronary tree, had accumulated in the right atrium.

The rest of the protocol was essentially similar for both experimental groups and was identical with that described in our prior report.[5] Bilateral thoracotomy was performed through the fourth intercostal space. Following venous and aortic occlusion, cardiac arrest was produced by the injection of a solution of 25 per cent potassium citrate (2 ml.), normal saline (18 ml.), and heparin (0.5 ml.) containing K^{42}.* Prior to injection, the radioactivity of the solution was determined by placing the loaded syringe beneath a scintillation tube. Following the induction of cardiac standstill and during the entire process of resuscitation, radioactivity of the heart was recorded. A sodium iodide, thallium detector for gamma rays (Nuclear Chicago), which fed into a count rate meter and this, in turn, into a linear and logarithmic recorder, was used for the purpose. During standstill, a piece of myocardium, M_1, was removed from the right ventricular wall for later study. After 6 minutes of venous inflow occlusion in Group II, coronary perfusion, which was maintained during this period, was stopped, caval clamps were released, and cardiac massage was begun. When a stable plateau of activity over the heart was observed, a second sample of myocardium, M_2, was removed from the right ventricle and the experiment was terminated by sacrificing the animals.

At autopsy, the heart was removed and its radioactivity was again determined to eliminate all possibility of an overlapping of counts from organs

*From Oak Ridge National Laboratory (10 millicuries in approximately 1 ml. of solution).

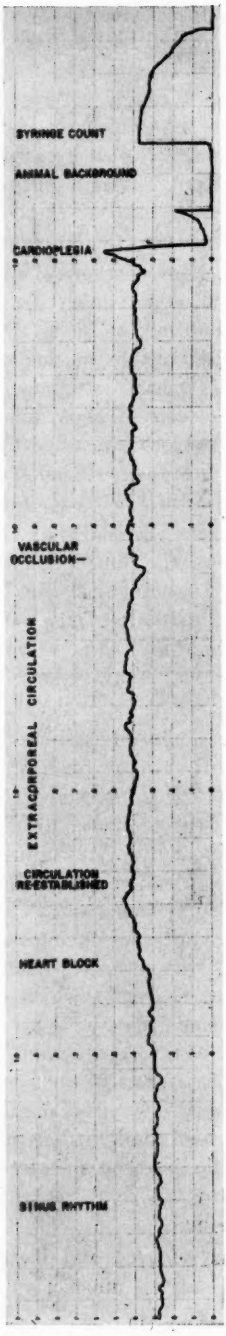

Fig. 1.—K^{42} (counts/min.) in the heart during and after cardioplegia with total cardiac bypass. (Read from right to left.)

other than the heart which might have occurred in vivo. The left and right ventricular myocardium, atria, and the septum were separated from each other and were individually examined for radioactivity. For that purpose, a subminiature probe counter tube* was employed. This is a stainless steel thin-walled counter which has a small sensitive volume and generates pulses, the amplitude of which are large enough to drive a scaler without need of a pre-amplifier. The probe was connected to a scaler and this in turn to a continuous graph recorder. It was introduced for a distance of 1 cm. into the depth of the myocardial segments. Separate recordings were made from the upper, middle, and lower thirds of the ventricular septa. Pieces of lung, liver, and kidneys were taken for determination of radioactivity. All samples were dried for 24 hours in a 100° C. forced draft oven prior to counting. Serial determinations of serum potassium, blood pH, and K^{42} activity in peripheral blood were made before and after cardiac standstill. The electrocardiogram was continuously monitored in all experiments.

RESULTS

Total Cardiac Bypass (GROUP I).—

The 16 animals in this group were subjected to 20 minutes of cardiac bypass at the onset of which cardioplegia was produced by an average of 12 ml. of the potassium solution having an activity of 5.1 million counts per milliliter per minute. A typical tracing depicting the radioactivity of the heart during and after cardioplegia with bypass is shown in Fig. 1. The sharp ascending limb, due to the proximity of the loaded syringe to the heart during injection, was followed by a descending slope associated with withdrawal of the syringe. Radioactivity remained fairly constant during the period of vascular occlusion and cardiac bypass. Upon removal of the aortic clamp a gradual descent of the tracing was observed. In this group, during occlusion an average of 3,200 counts/min. (100 per cent) was obtained by scanning over the heart. Immediately after removal of the clamps, activity was found to be 97 per cent (3,100 counts/min.) of the counts obtained during total bypass. At the onset of cardiographic evidence of electrical activity, the radioactivity was 2,900 counts/min. (89 per cent), and by the end of the experiments an average activity of 69 per cent (2,200 counts/min.) was detected. Thus, as in all previous groups observed, a substantial amount of the injected cardioplegic solution remained in the heart and was not associated with the return of normal rhythm. In this group only 1 animal failed to return to normal cardiac action before sacrifice. A residual activity of 65 per cent was observed in this dog.

A mean activity of 47,000 counts/gram/min. was demonstrated in the M_1 sample taken from all animals. From a knowledge of the weight of the heart, it may be estimated that approximately 90 per cent of the potassium injected is necessary to produce cardioplegia. This has been a constant finding. The activity of the second sample, M_2, taken at the termination of the experiment, was 21,000 counts/gram/min., or 44 per cent of the potassium injected to induce standstill.

*Anton Electronic Laboratories, Inc., Brooklyn, N. Y.

With release of the aortic clamp there was a slow increase of radioactivity in the peripheral blood. Within 1 minute following the appearance of electrical activity on the cardiogram, every animal demonstrated an abrupt augmentation of K^{42} in the peripheral blood. When normal sinus rhythm resumed, a still further increase occurred for a short period, and then a steady decline was observed, so that, by termination of the experiment, 37 per cent of the activity detected in the first peripheral sample had disappeared.

The sample of coronary sinus blood taken after standstill was accomplished demonstrated an activity of 19,100 counts/ml./min. which represented 0.3 per cent of the amount of cardioplegic solution injected. This would indicate that during cardiotomy an insignificant amount of the injected potassium is aspirated by the coronary suction apparatus.

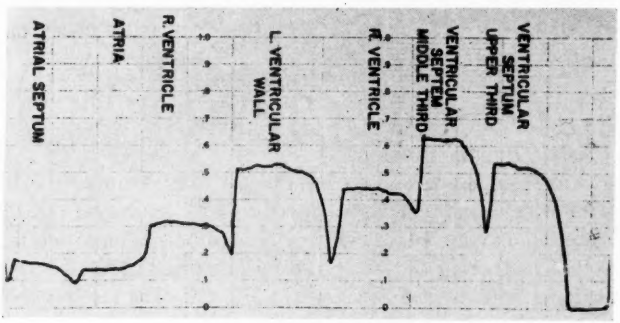

Fig. 2.—Residual K^{42} (counts/min.) in various areas of myocardium following cardioplegia and resuscitation using cardiac bypass.

The distribution of K^{42} detected in lung, kidney, and liver after sacrifice of animals was not uniform, there being 5,100, 2,900, and 800 counts/gram/min., respectively.

Measurement of radioactivity in various areas of the myocardium was carried out in vitro. A typical tracing is shown in Fig. 2. Average counts per minute of myocardium for all animals in this group were: left ventricle, 9,900; right ventricle, 8,800; atrium, 3,400; atrial septum, 4,200; upper third of the ventricular septum, 7,700; middle third, 11,100; and lower third, 8,700.

No change in blood pH was observed. Peripheral serum potassium averaged 3.7 before, 3.5 during, and 3.0 mEq./L. after cardiac bypass.

Hypothermia With Coronary Perfusion (GROUP II).—

An average of 13 ml. of potassium solution with a mean activity of 4.0 million counts per minute was necessary to produce cardioplegia in the 16 dogs of this group. A typical tracing demonstrating the changes in radioactivity of the heart during and after standstill and coronary perfusion is shown in Fig. 3. The pattern of activity observed is essentially similar to that reported for Group I, with one exception. Upon removal of the clamps in Group I, a gradual fall in radioactivity occurred, whereas, in this group, a more abrupt fall was observed. This may be attributed to cardiac massage expressing the potassium

from the vascular compartment. Radioactivity remained fairly constant during the period of vascular occlusion and coronary perfusion. Coronary perfusion under the conditions of these experiments failed to effect a change in the concentration of potassium in the stopped heart, but, with removal of caval and aortic clamps, a drop in activity was observed. This decrease was continued with cardiac massage. As previously reported, both Figs. 1 and 3 demonstrate that the activity of the heart is independent of the concentration of potassium in the myocardium. From Fig. 3 it is observed that ventricular fibrillation, heart block, and sinus rhythm all occurred while the radioactivity remained constant.

During occlusion in the 16 dogs an average of 2,700 counts/min. was detected over the heart in situ. This was considered as 100 per cent of activity.

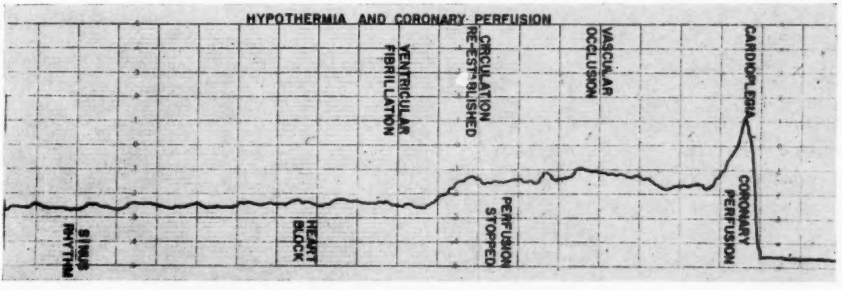

Fig. 3.—K^{42} (counts/min.) in the heart during and after cardioplegia with hypothermia and coronary perfusion. (Read from right to left.)

With cardiac massage, activity decreased to an average of 2,300 counts/min. (85 per cent of K^{42} injected). When cardiographic evidence of electrical activity was apparent, an average of 2,100 counts/min. (73 per cent of original activity) was present. This occurred at a mean time of 5 minutes after release of the occlusion clamps. At the termination of experiments, an average of 68 per cent of the original K^{42} (1,900 counts/min.) was obtained.

The first sample taken from the myocardium, M_1, which was considered representative of potassium incorporated during inflow occlusion, averaged 36,900 counts/gram/min. of heart muscle. The M_2 sample taken at the termination of the experiment averaged 13,500 counts/gram/min. of heart muscle. This represented 36 per cent of the activity incorporated into the myocardium at the time of occlusion. The apparent discrepancy between the activity detected at the end of the experiment by scanning over the heart (68 per cent of injected K^{42}) and counts obtained from the M_2 sample (36 per cent of potassium incorporated in the myocardium) is due to the fact that the former refers to radioactive counts per minute and the latter counts per gram per minute. Radioactivity was present, although not uniformly, in every organ assayed. At the termination of all experiments, specimens of lung contained an average of 5,900 counts/gram/min., kidney 2,500 counts/gram/min., and liver 1,697 counts/gram/min. Since no difference in activity of the various organs was observed in

animals which had resumed normal rhythm and in those failing to do so, it is suggested that the cardiac massage was effective in re-establishing a fairly normal circulatory state.

The coronary sinus blood, including that coming from the coronary perfusion and the excess of the injected potassium solution, was collected and an aliquot was assayed for activity. An average of 15,800 counts/ml./min. was obtained. As in Group I, this represents 0.3 per cent of the injected cardioplegic agent.

As previously reported for hypothermic animals without coronary perfusion, an abrupt increase in K^{42} was detected in peripheral blood samples with removal of caval and aortic clamps. A peak of radioactivity occurred within 2 minutes after the onset of cardiac massage, and there was then a progressive gradual decline in the number of counts per sample. An average of 89 per cent of the K^{42} activity obtained in the first assay of peripheral blood had disappeared

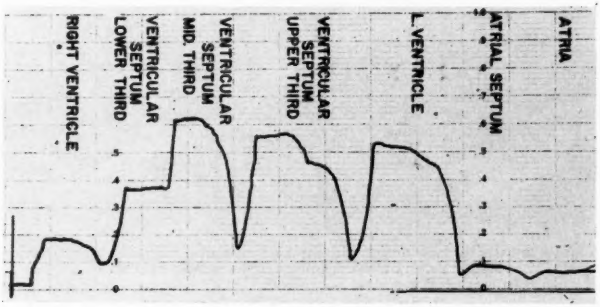

Fig. 4.—Residual K^{42} (counts/min.) activity in various areas of myocardium following cardioplegia and resuscitation using hypothermia and coronary perfusion.

by the end of the experiments. No significant change in blood pH occurred at any time. With re-establishment of venous inflow, a slight elevation of serum potassium (7.0 mEq./L.) was encountered, but this promptly returned to the pre-occlusion level (5.0 mEq./L.). As evidenced by electrocardiographic tracings, 8 of the dogs returned to normal cardiac activity before termination of the experiments and sacrifice of the animals.

After sacrifice, the heart was removed. Atrial and ventricular myocardium and septum were separated and were individually assayed for radioactivity as in Group I. A typical tracing appears in Fig. 4. The average counts per minute for the 16 animals were 6,600 for the left ventricle, 2,400 for the right ventricle, and 900 for the atrium. The atrial septum yielded 1,200, the upper one third of the ventricular septum 7,500, the middle one third 8,700, and the lower one third 5,700 counts/min.

DISCUSSION

Previous studies by us demonstrated that when potassium was used as a cardioplegic agent in normothermic and hypothermic animals, reversibility to

normal cardiac action was independent of the kinetics of this ion during resuscitation. Observations recorded in this paper confirm our earlier findings, for total cardiac bypass and hypothermia with coronary perfusion during cardioplegia likewise failed to establish a relationship between the "washing out" of potassium and the recovery of cardiac function. It would seem that potassium arrest has so altered the heart that merely removing occlusion clamps and permitting blood to flow through the coronary system is in most instances insufficient for a return to normal rhythm.

The dynamic activity of the potassium ion and its intimate connection with cell membrane permeability must be considered. It is well known that the concentration of potassium ion and its intracellular-extracellular gradient plays an important role in the sequence of events related to electrical potential of the cell membrane. This relationship between the extracellular potassium and the transmembrane potential has been expressed in terms of the mathematical equation $E = \log \frac{[Ki]}{[Ko]}$.* Thus, it may be seen how, by the injection of the cardioplegic solution (increasing Ko), this equilibrium might be altered. That such an imbalance can be accomplished without damage seems extremely unlikely, for unless a normal equilibrium of potassium ion is rapidly re-established on both sides of the cell membrane, and electric potentials reverted to normal, it is difficult to visualize a return to effective cardiac action.

It has been demonstrated that the distribution of potassium between intracellular and extracellular fluids in living tissues is largely controlled by the cells themselves.[7] Yet, this factor of self-regulation is probably dependent upon a normal cardiac action, for it has been demonstrated in these experiments that it was such an action—and not the mere mechanical work of the pump—which was effective in eliminating potassium from the myocardium. While there was an increase of K^{42} in peripheral blood immediately upon release of occlusion clamps, in every experiment there was a further increase with the onset of some kind of cardiac activity. This increase was further augmented subsequent to the resumption of a normal sinus rhythm. To break this cycle, that is, the interdependence of myocardial cell function and normal cardiac activity, in our experience maintenance of good coronary circulation has been considered to be mandatory.

Because Effler and colleagues[6] have stated that a high speed coronary flow will aid the heart in its recovery from cardioplegia, in several experiments following removal of occlusion clamps we increased the flow from 65 ml./kg./min. to 100 ml./kg./min. No difference in the speed of recovery or in the presence of arrhythmias was observed. While such perfusion might be expected to eliminate potassium in the vascular space, intracellular potassium cannot be eliminated by such mechanical means, for had such measures been effective, animals in Group II (coronary perfusion) might have been expected to demonstrate a greater amount of K^{42} in the atrial blood sample and a lesser activity in the M_1 myocardial sample.

*E = electropotential difference; Ki = intracellular potassium; Ko = extracellular potassium.

In these experiments a cardioplegic threshold was reached when an average of 40,000 counts of K^{42} was incorporated into each gram of myocardium. A greater amount of potassium is required to approach the cardioplegic threshold in clinical open heart surgery when long-standing disease has caused dilatation of the chambers and hypertrophy of the myocardium to three or four times the normal size. Since 44 per cent of the injected potassium in Group I and 36 per cent in Group II were found in the myocardium at the end of these experiments, it might well be expected that the amount of residual potassium in clinical cases will likewise be of larger magnitude.

Our studies have indicated that the remaining cardioplegic agent (potassium) cannot be indicated as the factor responsible for the production of temporary arrythmias, bundle branch block, fibrillation, etc. It is our impression that perhaps the only part of the procedure of induced standstill which is entirely a function of the amount of potassium injected is the cardioplegia itself. Events following the inception of standstill are influenced by factors which at present are unknown.

Elective cardiac arrest is often followed by cardiac arrhythmias. In Group I only 2 animals fibrillated, whereas, in Group II (coronary perfusion and hypothermia) 90 per cent of the dogs fibrillated one or more times after the reestablishment of the coronary flow. Electric shock was used for defibrillation. The 2 animals of Group I reverted to sinus rhythm immediately after defibrillation, whereas in Group II only 50 per cent reverted to sinus rhythm after demonstrating a variety of arrhythmias, the most common of which was heart time during resuscitation. Effler and colleagues[2] have reported that in several block. Thirty per cent of the dogs in Group I demonstrated heart block at some cases complete heart block has occurred when anatomic disruption of the conduction bundle seemed unlikely, and they attributed this to poor perfusion of the myocardium and surgical trauma. Melrose,[8] in discussing the same paper, stated that " . . . hearts will always start again provided they are not overstretched." In our experiments, surgical trauma was slight since little was done to the heart itself, coronary perfusion was satisfactory, overstretching of the myocardial fibers was avoided, and there was no anatomic disruption of the conduction system, since stitches were not placed near the septum. In spite of this, arrhythmias were not avoided during the period of resuscitation.

To evaluate the possible role of potassium as an etiologic factor producing these disturbances, the amount of this ion accumulated in various areas of the heart was determined. More K^{42} was found in the atrial septum than in the atrial myocardium; more in the ventricular septum than in the ventricular muscle; and a greater amount in the left than in the right ventricular wall. The greatest radioactivity was registered in the middle one third of the ventricular septum. Perhaps these differences may be due to a greater vascularity and larger muscle mass in the ventricular septum. Whatever the explanation, it would seem that frequent and persistent arrhythmias might be due to the greater amount of potassium accumulated in the path of the conducting system.

SUMMARY

Potassium is being used clinically as a cardioplegic agent in spite of limited physiologic knowledge concerning the fate of this ion. Previous studies by us in normothermic and hypothermic animals demonstrated that (a) reversibility of cardioplegia was not uniformly related to the amount of potassium injected or to its myocardial concentration, and (b) that "washing out" potassium did not imply a resumption of normal rhythm.

In this investigation, information was obtained concerning the fate of potassium (K^{42}) used as a cardioplegic agent in animals subjected to either total cardiac bypass or hypothermia with coronary perfusion. These studies, aside from adding confirmation to our previous findings, supply evidence that (1) once potassium induced cardioplegia is accomplished, its reversibility is largely beyond our control; (2) mechanical means are effective in "washing out" only the potassium accumulated in the vascular space and that re-establishment of normal intra- and extracellular equilibrium of this ion is dependent upon other factors; (3) there is an uneven distribution of potassium (K^{42}) within the heart, the greatest amount found in the middle one third of the ventricular septum, which might explain the frequent and persistent arrythmias which occur following the use of this agent; and (4) experimental data suggest that the indiscriminate use of potassium as a cardioplegic agent is hazardous.

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POSTOPERATIVE EAR OXIMETER STUDIES IN THORACOTOMY PATIENTS

II. Variations With Operative Procedures and With the Stir-up Regime

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INVESTIGATION of pulmonary physiology in post-thoracotomy patients has largely been concerned with the late results of resectional surgery or thoracoplasty. There are few reports of such studies in the immediate postoperative period. Hood and Beall[1] demonstrated arterial oxygen desaturation and respiratory acidosis developing in about 50 per cent of patients in the first hour after anesthesia. Alveolar hypoventilation was considered the major functional derangement. Mastio and Allbritten[2] extended such studies to the first postoperative day. They found that alveolar hypoventilation continued through the first postoperative day, and that both respiratory and metabolic acidosis developed following eight upper abdominal operations, and seven nonresective thoracic operations. Blair and Hickam,[3] in their study of intrapulmonary gas mixing, included data on lung volumes, minute ventilation, and maximum breathing capacity in the second week postoperatively in 5 lobectomy patients. They found normal ventilation by this time, but demonstrated increased impairment in intrapulmonary gas mixing. Our group recently made a preliminary report on arterial blood oxygen saturation for 10 consecutive postoperative days on patients undergoing pulmonary resections.[4] Saturations were found to be lowest on the second and third postoperative days. Extension of these studies should provide a more rational approach to the care of postoperative patients. To this end we have begun investigation of various parameters of pulmonary function. The purpose of this report is threefold: (1) to present in detail the daily oxygen saturation in patients undergoing various procedures, (2) to corroborate the value of the stir-up regime, and (3) to present certain arguments bearing on the mechanism of postoperative arterial blood oxygen desaturation.

METHODS AND MATERIAL

Sixty-two male patients undergoing 63 thoracic operations for tuberculosis were studied. Arterial blood oxygen saturation was determined, using a single

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scale ear oximeter. The same ear piece was used throughout the study. The same two anesthesiologists performed the tests. The ear piece was allowed to warm the pinna of the ear until a constant reading was established, usually 5 to 10 minutes. The preoperative arterial blood oxygen saturation was determined either the day before the operation, or on the morning of the operation after the administration of only a belladonna alkaloid as preanesthetic medication. Postoperative determinations were made on the operative day and for 10 consecutive postoperative days. After the saturation at rest was recorded the patient was asked to take 3 or 4 deep breaths. A second reading was recorded when the galvanometer restabilized.

Twenty-six patients had operations consisting of resection of one or two segments of the lung. The raw surfaces of the remaining segments were covered with pleura as much as possible to decrease air leak. Two of this group had postoperative atelectasis, 1 requiring bronchoscopy. Two others had hemorrhage requiring re-operation. Saturations for the latter were recorded as days after the second operation. Only 3 patients received oxygen therapy longer than 24 hours, and none longer than 48 hours postoperatively. Narcotics were used discriminately to relieve pain and the stir-up regime was mandatory.

Twenty-three patients underwent excision of a pulmonary lobe. Six of this group had atelectasis, 2 requiring bronchoscopies. One additional patient had atelectasis and pneumonitis requiring continued oxygen therapy. He died of respiratory insufficiency on the tenth postoperative day. No other patient required oxygen therapy beyond 36 hours. Narcotic administration and nursing care were comparable to the first group.

Thirteen patients underwent more extensive procedures, including pneumonectomy, thoracoplasty, extensive decortication, and plombage. These patients were grouped together as miscellaneous procedures, both out of statistical necessity, and because it was thought there was a greater compromise of lung tissue than with the previous two groups. There was one death, 2 days postpneumonectomy, and 2 cases of atelectasis not requiring bronchoscopy. No patient required oxygen after 36 hours, except 1 who was moribund. In this group, also, narcotic administrations were individualized and frequent stir-ups demanded.

RESULTS

The daily saturations and standard deviations of each of the three groups and of the entire group are presented in Table I. The distribution of individual saturations within each group was far from the "normal curve," being skewed with the tail toward desaturation. The standard deviations quoted are therefore large, but do provide an estimate of the range of the individual saturations. The highest saturations were recorded on the operative day in all three groups. This is a reflection of the routine administration of oxygen therapy on this day. Oxygen saturations decreased for 48 hours. Thereafter the average saturation for the lobectomy and segmental resection group tended to rise slowly toward normal at the end of a week. Patients undergoing more severe operations had lower saturations and did not attain preoperative levels within the first 10 days

of the study. There was a tendency observed with the lobectomy patients to have a slightly higher saturation on any given day than those patients undergoing segmental resections. The higher preoperative and operative day averages of the lobectomy group suggest that this may be due in part to a systematic error in the measurements. However, the greater variance of the segmentectomy group support a conclusion of greater disability for many patients in this group.

TABLE I. DAILY ARTERIAL OXYGEN SATURATION

OPERATION	PREOP.	DAY OF OPERATION	POSTOPERATIVE DAY 1	2	3	4	5	6	7	8	9	10
23 Lobectomy												
Average saturation	94.8	97.2	92.6	90.5	92.8	93.5	91.6	93.4	93.5	95.0	94.6	93.2
± S. D.	3.3	3.0	4.9	5.8	3.8	3.0	3.8	3.4	5.0	2.7	3.6	4.1
26 Segmental resection												
Average saturation	92.8	95.8	92.1	89.2	91.1	91.3	92.6	91.4	92.7	93.3	94.0	94.0
± S. D.	5.58	3.75	4.8	5.8	5.7	5.3	4.8	4.4	3.4	3.4	4.0	2.5
14 Miscellaneous												
Average saturation	92.5	95.8	92.8	87.4	88.7	92.2	89.8	90.1	91.3	90.7	89.6	90.5
± S. D.	4.4	3.6	4.0	9.6	7.2	3.5	5.9	5.6	6.3	3.5	8.0	6.4
Average of 63 operations												
Average saturation	93.5	96.2	92.5	89.3	91.2	92.4	91.6	91.9	92.8	93.5	93.4	93.0
± S. D.	4.8	5.9	4.7	6.9	5.5	4.3	4.9	4.3	4.7	3.7	5.1	4.4

TABLE II. CHANGE IN SATURATION WITH 3 TO 4 DEEP BREATHS

OPERATION	PREOP.	POSTOPERATIVE DAY 1	2	3	4	5	6	7	8	9	10
Lobectomy											
On air	94.8	92.2	90.9	92.7	93.6	91.5	93.4	93.5	95.0	94.6	93.2
After 3 to 4 deep breaths		96.3	94.8	95.4	95.8	95.1	96.0	96.0	96.4	96.4	95.1
Rise in saturation*		4.1	3.9	2.7	2.2	3.6	2.6	2.5	1.4	1.8	1.9
Segmental resection											
On air	93.7	91.2	89.2	91.1	91.2	92.6	91.4	92.7	93.3	94.0	94.0
After 3 to 4 deep breaths		95.0	94.1	94.5	93.1	95.6	94.0	95.5	95.8	96.1	95.7
Rise in saturation*		3.8	4.9	3.4	1.9	3.0	2.6	2.8	2.5	2.1	1.7
Miscellaneous											
On air	93.7	91.5	87.2	88.7	92.2	89.8	90.1	91.3	90.7	89.6	90.6
After 3 to 4 deep breaths		94.4	91.9	92.9	94.8	93.5	93.6	95.0	94.4	93.1	93.2
Rise in saturation*		2.9	4.7	4.2	2.6	3.7	3.5	3.7	3.7	3.5	2.6

*Significant at the 1 per cent level in all days and all groups.

There was a greater tendency for the segmental resection patients to exhibit higher saturations than the miscellaneous group. These observations were obscured somewhat by the wide scatter of the saturations in each group, but when the entire postoperative period is examined, the difference between lobectomy and segmentectomy patients, and between segmentectomy and miscellaneous procedures is significant (P less than 0.02 per cent).

Table II presents the change in saturation measured after 3 or 4 breaths. Only patient-days without oxygen therapy were included in this compilation. P values were calculated by Student "t" test. The rise in saturation after these few deep breaths is striking and highly significant (P less than 0.001). The increase was in part dependent on the degree of resting desaturation. The greatest increase was on the second and third postoperative day when saturations were lowest, averaging 3.9 to 4.9 per cent increase. All three groups showed comparable increases.

Ten patients had clinical and/or roentgen signs of atelectasis. The day on which the patients underwent bronchoscopies or on which they were given a "tracheobronchial toilet" or other definitive therapy, was designated as a "critical day." Table III presents the average oxygen saturations of these patients on the critical day and for 2 days before and after. The change in saturation from the day before to the day after the critical day is significant (P less than 0.05 per cent) even for this small group of patients.

TABLE III. SATURATIONS OF 10 PATIENTS WITH ATELECTASIS

	2 DAYS BEFORE CRITICAL DAY	1 DAY BEFORE CRITICAL DAY	CRITICAL DAY	1 DAY AFTER CRITICAL DAY	2 DAYS AFTER CRITICAL DAY
Resting saturation ± S.E.	90.1 1.3	88.9 1.7	90.0 1.6	93.7 1.2	93.4 1.5
After stir-up ± S.E.	93.1 3.7	92.0 2.1	93.4 1.7	96.0 1.3	95.9 0.7

DISCUSSION

There is a certain amount of stimulation and anxiety on the part of the patient which attends arterial puncture which would tend to mask hypoxemia if it were due to hypoventilation. The value of the single scale oximeter in estimating arterial blood oxygen saturations has been widely questioned. However, we feel that when it is used to compare day-to-day or minute-to-minute changes in the same patient, it is a clinically useful tool. Further, when large numbers of estimations are statistically grouped, the relative changes are thought to be quite reliable.

An average decrease in saturation could be produced by a few very desaturated patients. This was not the case in our patients. Fig. 1 shows the frequency distribution of saturations for the entire series over the 12-day period studied. It demonstrates that modal and median saturations are depressed in the first 72 hours postoperatively, and rise slowly in the next 7 days.

The desaturation described in our initial report might have been due to a disproportional desaturation attending a specific operative procedure. That this was not true is most clearly shown in Fig. 2. Although there is some difference between the values of each of the three operative groups, the similarity of the shapes of the graphs is striking. One would expect the technique of segmental resection to produce a greater although temporary alteration in pulmonary

function than the procedure of lobectomy. Our results substantiate such a view and are consistent with the anticipation of greater alterations in physiology following pneumonectomy, decortication, thoracoplasty, etc.

It is commonly observed that patients who seem to be doing well on the operative afternoon or on the first postoperative day may later develop pulmonary complications. This suggests there are progressive changes continuing for several days. The finding of lower saturation on the second and third days than on the operative or first postoperative day is evidence for such continuing changes. To be sure, many patients developed minimal desaturation in the first several days, but many others had marked desaturation. Clinically evident

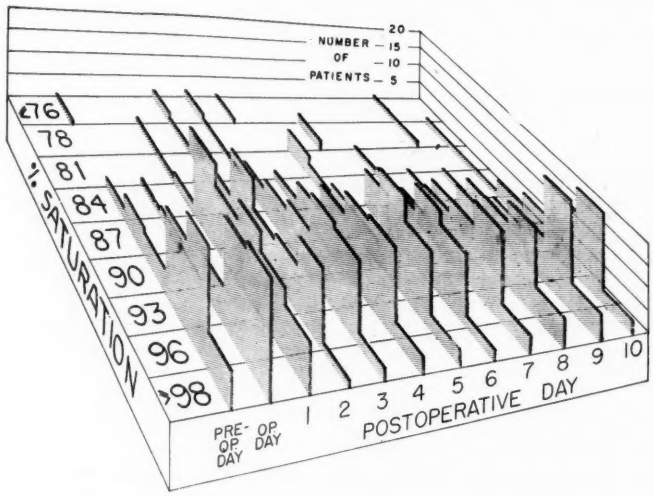

Fig. 1.—Three-dimensional histogram of the day-to-day saturations. One the horizontal axis extending back into the distance the saturations have been pooled into groups of 3 per cent. The heights of the histograms represent the number of patients with saturations in the indicated 3 per cent interval. The skewed distribution of the values is evident. This diagram demonstrates that the trend to desaturation is a general one, although there may be considerable difference in degree of desaturation from patient to patient.

cyanosis was uncommon except in the very ill. Desaturation on the second or third day was not predictive of subsequent complications or prolonged morbidity. Some patients with saturations in the range of 85 to 90 per cent did not have clinically evident complications. But certainly any patient with decreased arterial oxygen content runs a greater risk of complication.

There are three points that can be made from these data. (1) More extensive surgery seems to produce more extensive alteration in function. (2) Therapy directed specifically toward pulmonary complications is effective. This is demonstrated both by the increase in oxygen saturation following 2 or 3 deep breaths, and by the increase in saturation in those patients with atelectasis, following bronchoscopy, tracheobronchial toilet, etc. (3) Whatever alteration in function may be responsible for the desaturation, it is in large part reversed

by a few voluntary deep breaths. Inspection of Fig. 3 shows an almost uniform saturation reached after 3 or 4 deep breaths, no matter what day or what the resting saturation might be.

At our altitude, normal alveolar pO_2 is approximately 100 to 110 mm. Hg. This cannot be increased except by oxygen therapy or by hyperventilation sufficient and prolonged enough to lower significantly the alveolar pCO_2. Even if

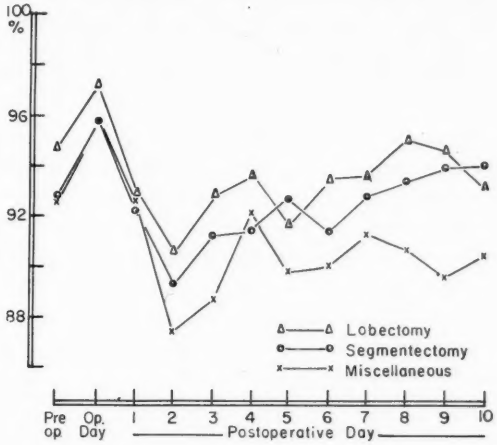

Fig. 2.—Average saturations in three groups of patients undergoing open thoracotomy.

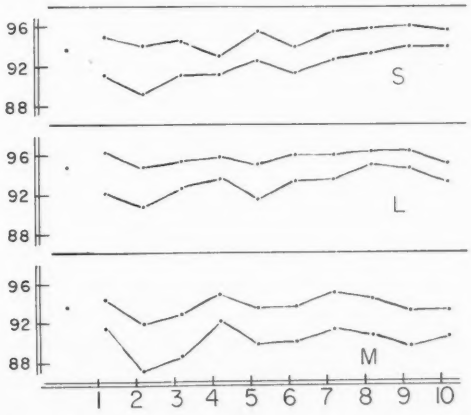

Fig. 3.—Comparison of average saturations in three groups of patients before and after 3 or 4 deep breaths. No patient receiving oxygen was included in this compilation. The preoperative average saturation is represented by a dot at the left of each pair of graphs. The groups are identified by: *L*—lobectomy, *S*—segmental resection, *M*—miscellaneous procedures.

the deep breathing utilized in this experiment were sufficient to lower the pCO_2, it would have returned toward the initial level by the time the oximeter was recalibrated. Therefore, the rise in saturation must be due in greatest part to a mechanism which does not involve a supranormal alveolar pO_2.

Diffuse subclinical atelectasis has been suggested as a possible mechanism of arterial desaturation in postoperative patients. One would not expect 3 or 4 deep breaths to re-expand large portions of such atelectatic areas. Nor would elevation of alveolar pO_2 with oxygen therapy in such circumstances result in significant elevation of arterial blood oxygen saturation. Thus, the marked increase noted on the operative day is inconsistent with diffuse collapse at that time. In 10 patients with definite atelectasis, specific therapy directed toward the complication was found to increase the saturation significantly. An increase in saturation with deep breathing was noted both before and after resolution of the atelectasis. This indicates that there were additional mechanisms for desaturation.

Reduction in diffusion capacity of the lung for oxygen has also been suggested as another mechanism for desaturation.[4] The normal diffusing capacity for oxygen is approximately 20 to 25 c.c. O_2/minute/mm. Hg/M.^{2} body surface. It would require a reduction of 75 per cent to produce the observed saturations in the average patient, i.e., an increase in driving pressure gradient of oxygen of 400 per cent. From the flattening of the oxygen-hemoglobin dissociation curve above 90 per cent saturation, one must conclude that a rise in arterial saturation of the magnitude observed after deep breathing would be possible only with a supranormal alveolar pO_2, if a diffusion defect were the primary mechanism involved. If there were a diffusion defect in these patients, it was neither very great nor responsible for the observed desaturation.

Possible mechanisms for arterial desaturation include alveolar hypoventilation with either depression of the central nervous system or mechanical impairment including pain, defects in intrapulmonary gas mixing, or alteration in the ventilation-perfusion ratio. Hypoventilation has been documented in the first 24 to 36 hours postoperatively[1, 2] and is the most probable cause of prolonged desaturation. More specific pulmonary function testing may confirm this view and indicate the relative importance of depression, pain, and mechanics.

SUMMARY

The day-to-day oxygen saturations in 63 open thoracotomy cases are presented. The three surgical groups, lobectomy, segmental resection, and miscellaneous procedures, were shown to be qualitatively similar with greatest desaturation in the second postoperative day and improvement slowly thereafter. Quantitatively, the miscellaneous group exhibited the greatest desaturation and the lobectomy group the least, but the segmentectomy group had the most rapid recovery. Saturations in all three groups after a few deep breaths were found to approach normal. This excludes diffuse subclinical atelectasis and defects in diffusion in the lung as likely mechanisms producing the arterial saturations observed.

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TECHNICAL PROBLEMS IN THE SURGICAL REPAIR OF INTRATHORACIC ANEURYSMS

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THE MAJOR problems associated with the surgical management of thoracic aortic aneurysms are concerned either with vascular occlusion required during the course of the repair or with technical aspects of the actual repair. Whether or not complete vascular occlusion is required depends upon both the type of aneurysm present and the kind of repair utilized. For example, a saccular aneurysm in which the neck can be isolated, clamped, and sutured will not necessitate complete occlusion of the aorta, while a fusiform or large saccular one which is to be completely excised and replaced with a suitable graft will require complete proximal and distal occlusion.

The ill effects of cross-clamping the aorta arise from the increased pressure which results proximal to the occlusion and/or from the decreased pressure and resultant decreased blood flow distal to the occlusion. The degree of hypertension which occurs proximal to the occlusion depends upon the level of the occlusion. Cross-clamping the arch of the aorta produces a greater increase in proximal pressure than clamping the aorta just above the diaphragm. The more proximal cross-clampings may produce such a high pressure and increased resistance that acute heart failure or cerebrovascular accident may be precipitated.

Of more common occurrence are the results of decreased blood flow distal to the occluded segment. The tissues of the central nervous system are most sensitive to ischemia. Occlusion proximal to the left common carotid artery may produce hemiplegia, although not infrequently good blood flow through one common carotid artery may be sufficient to nourish the entire brain. One of the greatest hazards of thoracic aortic occlusion is the risk of spinal cord ischemia, since the chief components of the anterior spinal artery are composed of the radicular branches from the thoracic aorta.[1]

Clinical experiences with the length of time during which the descending thoracic aorta may be safely occluded have varied. Crafoord[2] successfully occluded the aorta for 27 minutes while repairing a patent ductus arteriosus, while Chamberlain[3] stated that neurologic damage may follow occlusion for 24 minutes. Adams[1] recently gave 18 minutes as probably the maximum safe occlusion time. In our own experience, paraplegia resulted from a 13-minute

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occlusion associated with the insertion of a Hufnagel valve, although in this instance ligation of three pairs of intercostal arteries may have contributed to the spinal cord ischemia.

Since other tissues are normally much less sensitive to hypoxia than nervous tissue, measures taken to avoid cord damage usually are adequate to protect the kidneys and other tissues within the abdomen.

One very serious hazard which is probably the result of peripheral hypoxia is the diminished peripheral resistance which not infrequently follows periods of aortic occlusion. Severe hypotension may occur as the occluding clamp is released, in spite of releasing the clamp slowly and in spite of adequate blood replacement and/or vasopressor agents.

Surgical exposure must be wide enough to allow an approach to the aorta at a safe distance from the aneurysm, both proximally and distally. The aorta should be exposed on each side of the aneurysm prior to dissection near it since, if the aneurysm is inadvertently entered, prompt control is mandatory.[4] We have favored bilateral anterior thoracotomy with median sternotomy for aneurysms of the ascending aorta or arch, although other approaches may be used.[5] Closure of the wounds has not been a problem and disruption has occurred in only one instance, following extensive mediastinitis.

The following case histories, most with an unfavorable outcome, have been selected from our experiences to illustrate some of the more common problems which arise in management of the various types of thoracic aneurysms.

CASE REPORTS

A. *Aneurysm of Ascending Aorta.*—

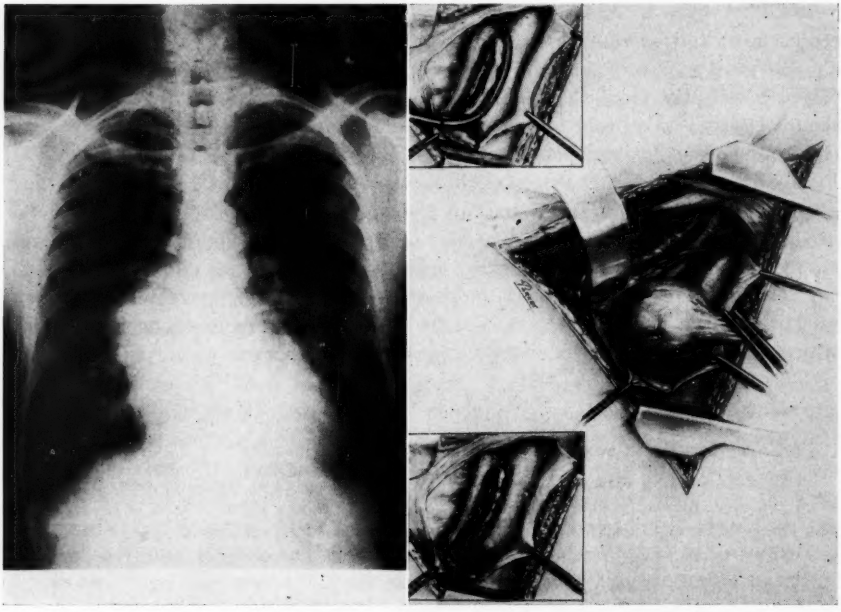
CASE 1.—J. G., a 44-year-old Negro man, had an orange-sized syphilitic aneurysm arising from the ascending aorta and projecting anterolaterally to the right (Fig. 1, *A*). Exposure was obtained through a right anterior thoracotomy in the third intercostal space with median sternotomy to the jugular notch. The aneurysmal neck was occluded easily with a cloth-covered intestinal clamp, enabling excision and repair with interrupted No. 3-0 silk sutures (Fig. 1, *B*). The ascending aorta was thus reconstructed to a normal diameter.

CASE 2.—J. C., a 45-year-old white man, had a syphilitic aneurysm involving the left aspect of the ascending aorta and inferior aspect of the arch (Fig. 2, *A* and *B*). The large, grapefruit-sized aneurysm was quite adherent to the trachea posteriorly and pulmonary artery anteriorly. Anatomically, this sac was so situated and its neck was so wide that it could not have been managed by means of a lateral reconstruction without aortic occlusion. It was planned to use a temporary shunt enabling aortic occlusion with reconstruction of the arch; however, the sac was inadvertently entered at the junction of the sac and ascending aorta. Massive bleeding which followed was controlled by placing a clamp parallel to the ascending aorta on the neck of the aneurysm and across the aortic arch distal to the innominate artery. Cardiac arrest occurred but with rapid blood replacement and cardiac massage an effective heartbeat was restored. With the arch occluded and blood flowing to the brain through the right innominate artery, the inferior aspect of the arch was reconstructed (Fig. 2, *C*). Although the patient survived the surgery, he died later from cerebral damage.

The successful management of this type of aneurysm necessitates measures to avoid cerebral ischemia. In 1 patient, operated upon with Dr. Mark Wolcott at the Veterans Administration Hospital, the innominate and left common

carotid arteries were occluded 15 minutes during a restorative endoaneurysmorrhaphy. Blood flow to the brain was thus limited to the left vertebral artery during the repair. The patient survived without evidence of neurologic damage only to die later of other complications.

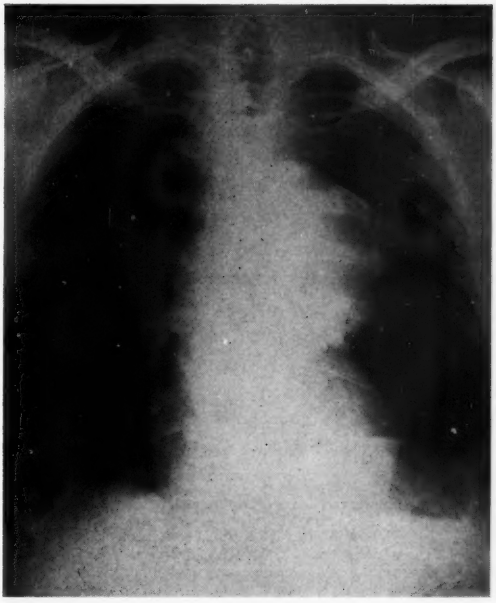
Hypothermia of a moderate degree (lower limit, 90° F.) adds considerable protection to the brain in aneurysms in this area. When the aneurysm is in the innominate artery and temporary occlusion of the left common carotid is necessary, hypothermia may be adequate to protect the brain.



A. *B.*

Fig. 1.—*A*, Posteroanterior x-ray of chest showing saccular aneurysm of ascending aorta. *B*, Lateral aortorrhaphy.

On the other hand when an aneurysm is as extensive as in Case 2, arch replacement probably should be the goal. This would necessitate a bypass shunt from ascending aorta to cerebral vessels and distal aorta. Considerable experimental and clinical studies have been presented by Izant,[6] Hardin,[7, 8] Stranahan,[9] Cooley,[10] and Creech[11] and their associates. The shunts must be of sufficient inside diameter to avoid increased resistance to flow, otherwise acute left heart failure may occur. Hardin and associates[8] demonstrated experimentally that the heart would not tolerate shunts of small diameter and that hypothermia and partial inflow stasis were necessary if small shunts were used. Stranahan[9] suggested shunts with an inside diameter of 10 mm. or larger in the presence of hypertension or coronary disease. During arch replacement, Cooley and associates[10] combined hypothermia and a shunt with an inside



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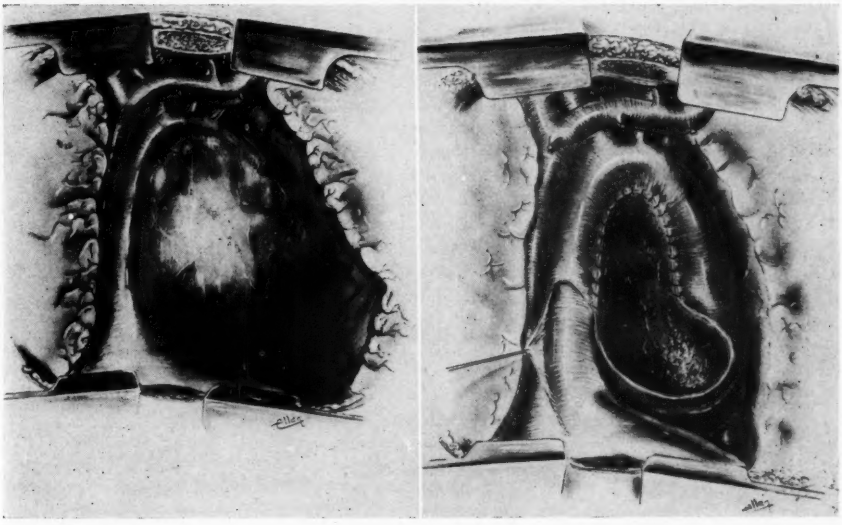


B. *C.*

Fig. 2.—*A*, Posteroanterior x-ray of chest which shows large aneurysm arising from inferior aspect of aortic arch. *B*, Drawing which shows large aneurysm arising from inferior aspect of aortic arch. *C*, Drawing which shows completed reconstructive aneurysmorrhaphy.

diameter of 14 mm. with fall in pressure distally of only 10 mm. Hg when the aorta was occluded. Without the use of hypothermia, larger shunts, probably up to 2 cm. in diameter, will be necessary.[11]

Recently De Bakey and associates[12, 13, 14] have presented another approach to aortic aneurysms. During total cardiac bypass, using a modified DeWall-Lillehei pump-oxygenator, aneurysms of the ascending aorta and arch have been successfully operated upon.

B. *Aneurysms of Innominate Artery and Arch of Aorta.*—

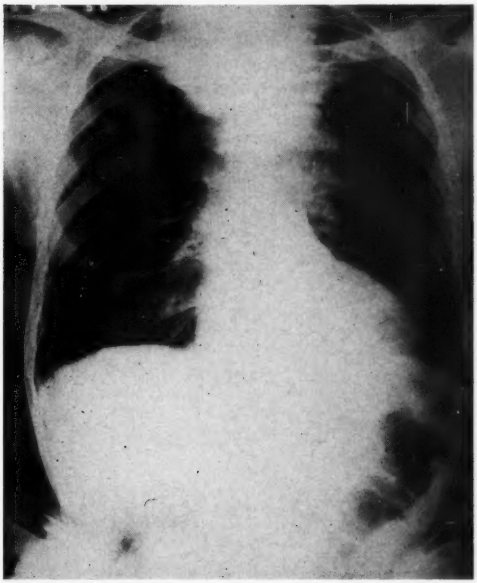
Aneurysms involving the innominate artery frequently can be satisfactorily managed by means of aneurysmectomy with ligation of the right subclavian and common carotid arteries. More often, however, there is associated involvement of the aortic arch or the aneurysm arises in the innominate adjacent to the arch so that there is a wide neck of several centimeters at the arch. In this area, aneurysms are densely adherent to the superior vena cava, innominate vein, and trachea, and frequently have eroded into the anterior chest wall. Such an aneurysm must be approached widely and extreme precautions are necessary in its mobilization until the proper time arrives to occlude its neck.[4] If the left common carotid artery is not involved it is usually densely adherent to the wall of the aneurysm and must be separated with care.

CASE 3.—J. J., a 65-year-old Negro man, had a saccular aneurysm of the innominate artery which filled the superior mediastinum and presented in the low anterior cervical region as a large orange-sized pulsating mass (Fig. 3, *A* and *B*). This aneurysm was approached through an anterior bilateral thoracotomy in the third intercostal space combined with median sternotomy to the jugular notch. Since it was necessary to occlude the left common carotid artery when the neck of the sac was occluded, a compressed Ivalon sponge graft* was placed from the side of the ascending aorta to the end of the divided right common carotid (Fig. 3, *C*). Cerebral blood flow was maintained through the left carotid for 50 minutes while the graft was placed on the right. Thereafter, cerebral flow was provided through the graft to the right common carotid for 40 minutes while the aneurysm was being removed. All of the aneurysm was removed except its posterior wall which was densely adherent to superior vena cava, trachea, and mediastinal tissues. Postoperatively, the patient developed an extensive mediastinitis which could have been related to the residual sac or the plastic prosthesis. Even though he had cerebral flow through one carotid artery at all times and eventually in both, right hemiparesis developed. This was improving when he began to deteriorate from mediastinal infection. His death resulted from exsanguination due to rupture of the aorta adjacent to the suture line at the base of the left common carotid artery.

It has been demonstrated by Bahnson[4] that sacrifice of the innominate artery is tolerated unusually well; in one paper he mentions that this had been done in 5 patients without sequelae. There is an approximate mortality of only 5 per cent with ligation of one carotid artery but a morbidity as high as 40 per cent.[15]

CASE 4.—T. B., a 50-year-old Negro man, had a very large innominate artery aneurysm which proximally involved the aortic arch and distally extended well into the neck (Fig. 4, *A*). The aneurysm was exposed through an anterior bilateral thoracotomy in the fourth intercostal space. It seemed to arise from the arch with a base of some 5 cm. Prior to dissecting around the aneurysm, a 2 cm. diameter temporary bypass shunt of compressed Ivalon sponge was sutured to the side of ascending aorta and descending aorta beyond the arch. About the midpoint of the Ivalon shunt was a T-limb into which was inserted a plastic Y adapter

*The use of compressed Ivalon sponge grafts has been discontinued.



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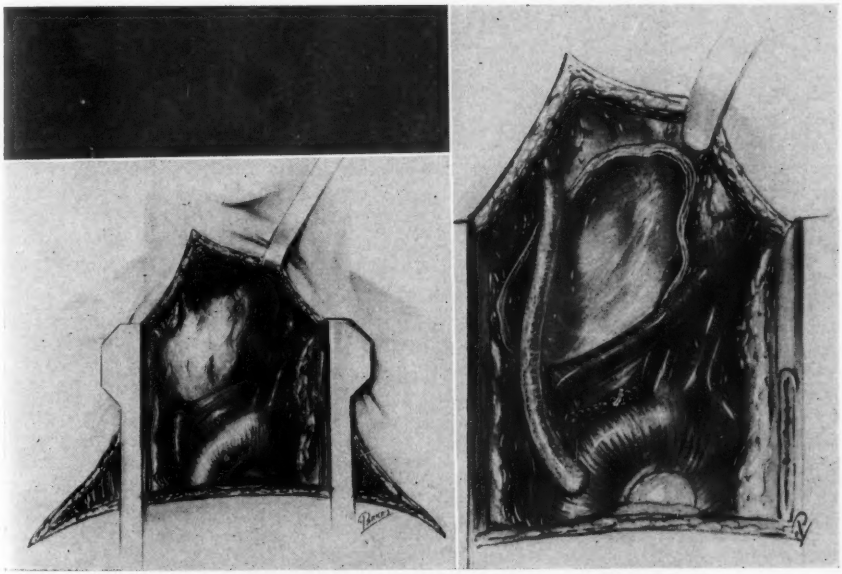
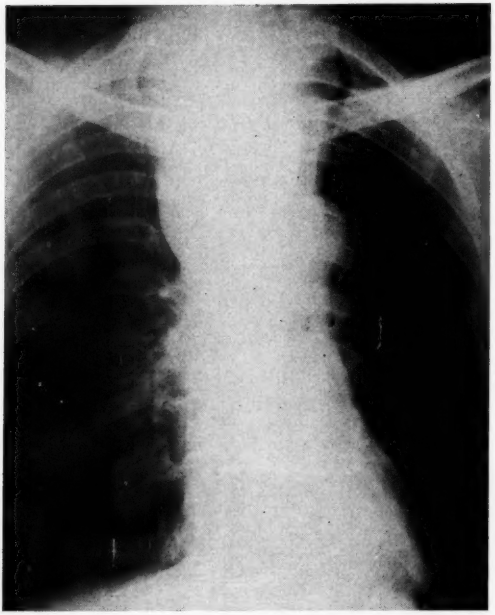


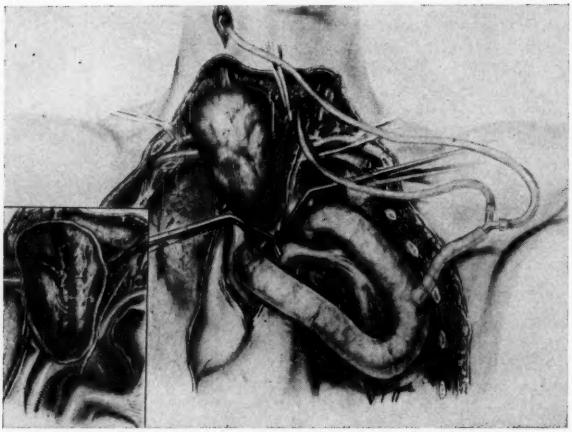
B. *C.*

Fig. 3.—*A*, Posteroanterior x-ray of chest which shows large aneurysm arising in innominate artery at its origin from the aortic arch. *B*, Drawing which shows large aneurysm arising in innominate artery at its origin from the aortic arch. *C*, Drawing which shows completed repair with compressed Ivalon graft from aortic arch to innominate artery.

with two No. 16 F. plastic catheters which were inserted into the carotid arteries, the right in the neck and the left within the thorax (Fig. 4, *B*). The arch was then isolated by occlusive clamps while circulation was maintained to all organs through the shunt. The femoral artery pressure, which was being monitored with a Statham transducer and Cambridge recorder, did not change with aortic occlusion and remained at about 100 mm. Hg systolic during the hour on the bypass. Cardiac function seemed good during the bypass, indicating



A.



B.

Fig. 4.—*A*, Posteroanterior x-ray of chest which shows innominate artery aneurysm extending into neck. *B*, Drawing which shows temporary bypass graft to provide blood flow to brain and distal organs during reconstruction of aorta.

that the size of the shunt was adequate. After aortic occlusion, the aneurysm was opened widely and evacuated of thrombus in varying stages of organization. The neck of the aneurysm was found to be 5 cm. in length, arising at the junction of the arch, innominate artery, and left common carotid arteries. Reconstruction was accomplished with continuous sutures of No. 2-0 silk in such a manner as to restore flow through all head arteries. Part of the sac wall was excised, but it did not seem feasible to attempt excision of the sac from its adherence to trachea, superior vena cava, and innominate artery. The bypass functioned well and technically the repair was satisfactory. During the latter part of the operation, oozing from all raw surfaces became quite severe, although bleeding had not been a problem earlier. The patient failed to respond to the usual measures and died in the recovery room several hours postoperatively while receiving the twenty-fifth pint of blood.

C. *Aneurysms of Descending Thoracic Aorta.*—

Complications as a result of occlusion of the descending thoracic aorta depend upon the level of occlusion, whether occluded at two levels simultaneously, duration of occlusion, division of intercostal arteries, and extent of collaterals.[1, 16, 17]

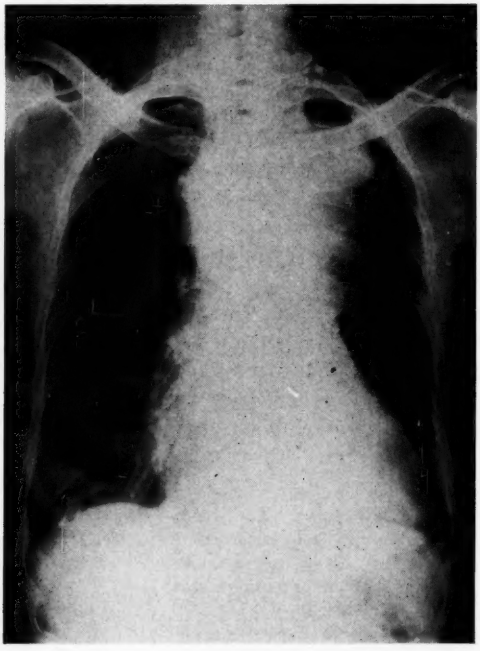
It has been demonstrated that the duration of aortic occlusion can be safely extended by the use of hypothermia[17] and, also, that the use of temporary or permanent bypass shunts eliminates the dangers of aortic occlusion.[3, 18] This does not, however, eliminate the dangers of cord ischemia as a result of ligation of intercostal arteries at the site of the aneurysm. It is entirely likely, however, that the presence of the aneurysm has stimulated the development of collaterals.

CASE 5.—M. W., a 65-year-old Negro woman, had a grapefruit-sized saccular aneurysm of the upper descending thoracic aorta. The aneurysm had eroded the thoracic vertebral bodies and compressed the trachea and esophagus (Fig. 5, *A*). Exposure was obtained through a bilateral thoracotomy. A compressed Ivalon graft, 2 cm. in diameter, was inserted by end-to-side anastomosis as a shunt from the arch to the distal descending aorta, allowing aneurysmectomy to be accomplished without haste (Fig. 5, *B*). The lower trachea was noted to be quite soft and flexible at the site of its compression. The patient tolerated the surgery well, but 18 hours later developed respiratory distress. The clinical picture suggested heart failure but therapy directed along these lines did not alter her deterioration. There was no significant elevation in blood pressure in the arms to suggest increased resistance from the shunt. Autopsy revealed pronounced pulmonary congestion consistent with heart failure and marked collapse of the lower trachea. Her death presumably was due to heart failure aggravated by hypoxia resulting from the collapsing trachea.

CASE 6.—O. K., a 60-year-old white man, had a long fusiform aneurysm involving two thirds of the descending thoracic aorta (Fig. 6, *A* and *B*). The surgical approach was through a long left parascapular incision with pleural entry through the bed of the resected fourth rib for mobilization of the proximal portion of the aneurysm and through the bed of the resected eighth rib for exposure distally. A permanent compressed Ivalon sponge graft was placed end-to-side between the arch and the supradiaphragmatic portion of the aorta, with subsequent aneurysmectomy (Fig. 6, *C* and *D*). The postoperative course was benign and the patient presented no evidence of neurologic damage. He was doing well when last seen 13 months after surgery.

Aneurysms in the distal thoracic aorta may make surgical repair quite hazardous because the great radicular artery to the anterior spinal artery arises at this level.[1, 19] It presumably arises in the eighth to twelfth thoracic segment and, if these intercostals have to be divided, serious neurologic sequelae may result. The presence of the aneurysm, however, with perhaps thrombosis of some of the intercostals, may provide adequate stimulus for development of collaterals. In the absence of a shunt or hypothermia, renal damage then becomes

of chief concern. De Bakey and Cooley,[20] however, reported no serious renal complications after occlusion of this portion of the aorta for 45 minutes during which an aneurysm was resected and a graft inserted.



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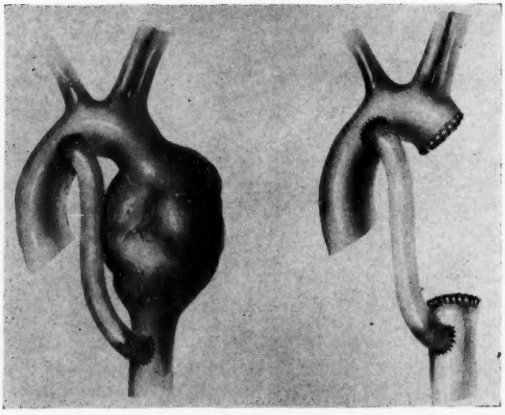
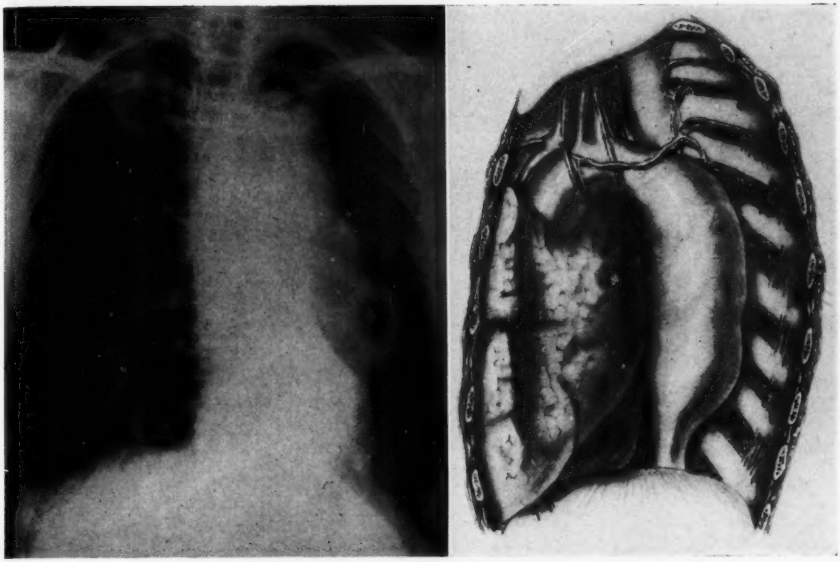
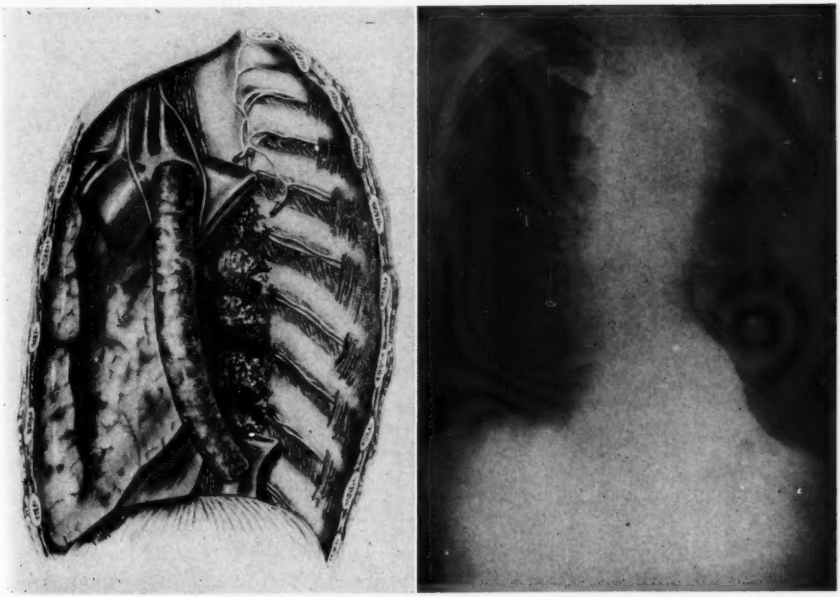


B.

Fig. 5.—*A*, Posteroanterior x-ray of chest which shows large aneurysm involving upper descending thoracic aorta. *B*, Drawing which shows permanent compressed Ivalon bypass graft.



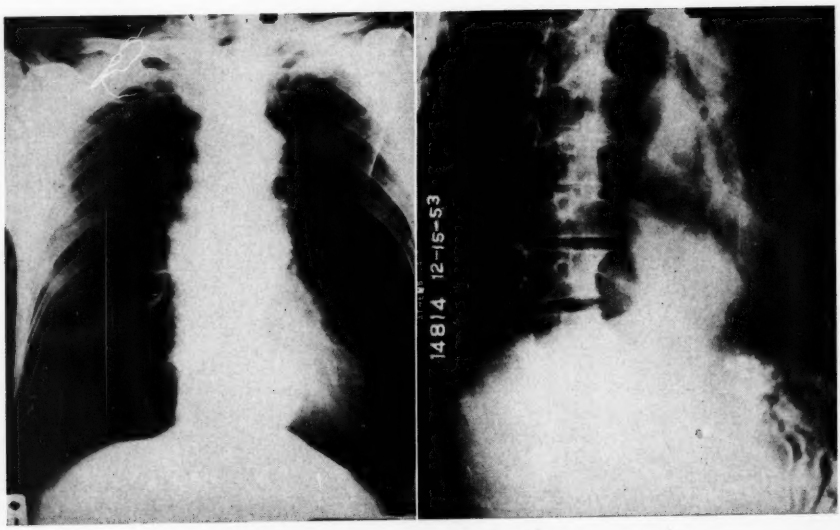
A. *B.*



C. *D.*

Fig. 6.—Posteroanterior x-ray of chest (*A*) and drawing (*B*) which show fusiform aneurysm involving two thirds of the descending thoracic aorta.

Drawing which shows permanent compressed Ivalon sponge bypass graft (*C*) and postoperative x-ray (*D*).



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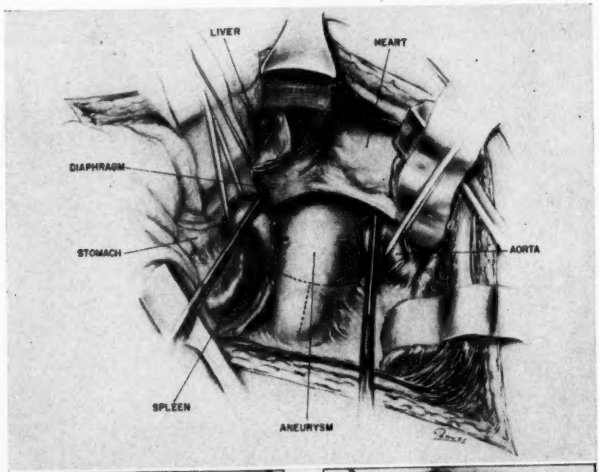

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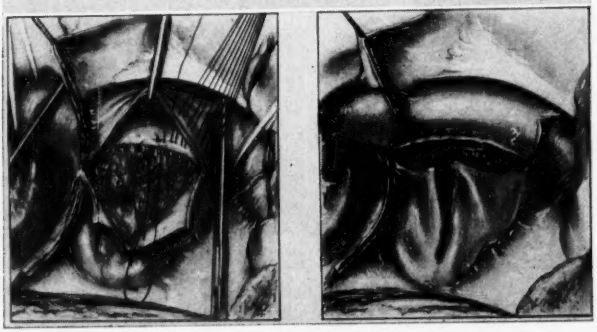


D.

Fig. 7.—*For legends see opposite page.*

CASE 7.—H. W., a 63-year-old white man, had a saccular aneurysm of the thoracic aorta just above the diaphragm (Fig. 7, *A* and *B*). It had eroded the eleventh and twelfth vertebral bodies. Exposure was obtained through a long left thoracoabdominal incision. After careful mobilization of the aorta just above and below the aneurysm, the aorta was occluded for 40 minutes while a restorative endoaneurysmorrhaphy was done. The excess sac was excised (Fig. 7, *C* and *D*). No neurologic damage was evident but the patient developed an

Fig. 8.—*A*, Aortogram showing fusiform aneurysm of ascending aorta and saccular aneurysm of upper descending aorta.

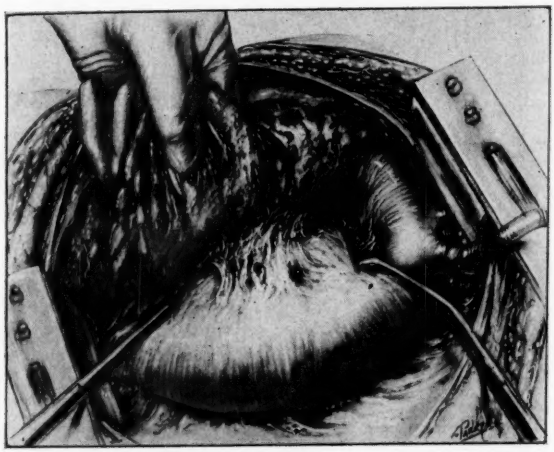
oliguria with an NPN elevated to 70 which had returned to normal when he had been dismissed 2 weeks postoperatively. An aortogram made by injection of 50 c.c. of 70 per cent Urokon intravenously, prior to dismissal, revealed that the reconstructed aorta had a slightly larger diameter than the aorta proximally. This discrepancy, of course, is undesirable because of the greater lateral pressure in this area. When the patient was seen recently, 3 years since the repair, he was found to have an aneurysm in the same area about the size of the original one. He refused surgery which would have consisted of replacement with a graft.

In such cases, a bypass graft anastomosed end-to-side to the aorta prior to excision of the aneurysm probably functions as well as one sutured end-to-end to the aorta. Since many of these patients have other serious organic diseases, the greater operating time in the latter case may work to a disadvantage for the patient.

CASE 8.—C. C., a 62-year-old white man, had a left exploratory thoracotomy performed elsewhere, because of suspected bronchogenic carcinoma. He was found to have a saccular aneurysm involving the upper descending thoracic aorta presenting into the hilus of the left

Fig. 7.—*A* and *B*, Posteroanterior and oblique x-rays showing saccular aneurysm just above the diaphragm and eroding the eleventh and twelfth vertebral bodies.
C and *D*, Drawings which show method of lateral reconstruction.

lung with obstruction of the left main-stem bronchus and partial atelectasis of the left lung. He was also found to have a smaller aneurysm of the ascending aorta. X-ray study, including angiocardiography, confirmed the presence of the two aneurysms (Fig. 8, *A*); because of symptoms of cough, wheezing and shortness of breath associated with bronchial obstruction, a surgical attack upon the more distal aneurysm seemed urgent. The aneurysm was exposed through a left posterolateral incision and proximal and distal control obtained by encircling umbilical cord tape. Partial cardiopulmonary bypass was utilized to provide adequate blood flow distally as well as to avoid the hazards of increased pressure in the proximal aortic



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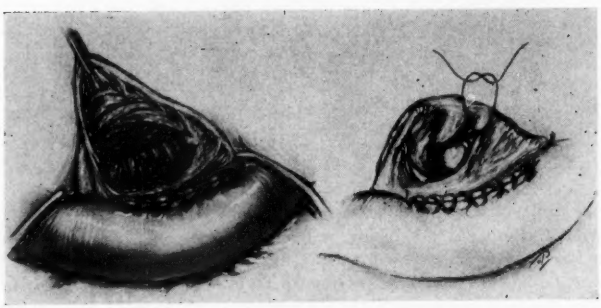

C.

Fig. 8.—Cont'd. *B* and *C*, Drawings which show saccular aneurysm of descending aorta extending into hilus of lung and eroding left main-stem bronchus.

segment during aortic occlusion.[14] For this purpose, a stainless steel cannula was placed in the left subclavian artery from which blood was pumped through a De Bakey roller pump into a femoral artery. Monitoring pressures were obtained through a catheter in the right radial and other femoral artery. During 50 minutes of partial bypass, the neck of the sac was mobilized and a lateral reconstruction accomplished. In the base of the sac, the left main-stem bronchus was identified with an ulcerated defect, 1 cm. in diameter. This defect was repaired by suturing a graft of Teflon cloth snugly over the defect which was reinforced by two layers of the tough aneurysmal sac (Fig. 8, *B* and *C*). The surgical procedure was tolerated extremely well and the postoperative course was benign. The left lung promptly re-expanded and symptoms associated with bronchial obstruction have been completely relieved.

SUMMARY

The major problems to be overcome in the surgical treatment of thoracic aortic aneurysms are concerned with the ill effects, both proximally and distally, of having to stop the flow of blood through that portion of the aorta, and with the technical aspects of the actual repair. Case histories of patients illustrating many of these difficulties are presented. Methods are presented which we have used in securing adequate surgical exposure, in avoiding some of the hazards associated with cross-clamping the aorta, and in carrying out the technical aspects of aortic replacements.

Further improvement in the results of surgery of this type is to be expected with simplification and more common usage of temporary bypassing shunts and with the utilization of pump-oxygenators in certain circumstances.

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PERFORATION OF THE RIGHT VENTRICLE DURING SELECTIVE ANGIOCARDIOGRAPHY

Report of a Case

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THE RECENT literature contains several reports attempting to evaluate the indications and technique of selective angiocardiography.[1-4] Critical evaluation of such a technique should include a consideration of the potential dangers and complications. Included in the rarer complications is perforation of the heart. The true incidence of this mishap is difficult to determine. Bagger and her associates,[1] in a review of 2,958 selective angiocardiograms from 12 Swedish hospitals, reported four instances of injection of contrast material into the right ventricular myocardium. Escher, Shapiro, Rubinstein, Hurwitt, and Schwartz[5] described actual perforation of the right ventricular apex with partial injection of contrast material into the pericardial cavity in a 27-year-old woman with isolated pulmonic stenosis. Cardiac tamponade ensued, necessitating pericardiotomy. Because selective angiocardiography is increasing in popularity in this country, the following case is deemed worthy of record.

CASE REPORT

The patient, a 26-month-old white female, was admitted to the hospital on Jan. 1, 1958, for evaluation of congenital heart disease. She was born following a full-term uneventful pregnancy. Birth weight was 6 pounds 11 ounces. Cyanosis was noted shortly after delivery. Development was slow, and repeated respiratory infections required frequent hospitalizations. The child did not walk until 2 years of age and was noted to squat when fatigued. The slightest exertion produced marked dyspnea and accentuated a persistent mild cyanosis.

Physical examination on admission revealed a pale, poorly developed, scrawny 2-year-old girl, weighing only 17 pounds. There was cyanosis of the lips and nail beds at rest. The chest was symmetrical and the lungs clear. Cardiac rate was 136 with a loud harsh systolic murmur audible over the third and fourth intercostal spaces along the left sternal border. A thrill accompanied the murmur. The pulmonic second sound was louder than the aortic. Femoral pulses were easily palpable. A smooth, nontender liver edge was felt 1 cm. below the right costal margin. There was clubbing of the fingers and toes but no peripheral edema. Hemoglobin was 16.1 Gm. with an hematocrit of 67 per cent. An electrocardiogram was interpreted as showing right ventricular hypertrophy. Fluoroscopic and radiographic examination of the chest with barium swallow demonstrated a right-sided aortic arch, marked right

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ventricular enlargement, and prominent pulmonary vessels. The cardiac waist appeared narrowed but it was difficult to determine how much of this could be attributed to the right-sided aorta.

On Jan. 21, 1959, a diagnostic cardiac catheterization and angiocardiogram were performed commencing at 1:30 P.M. Following sedation with 15 mg. of Demerol and 12.5 mg. of Phenergan, a No. 6 N.I.H. cardiac catheter was passed without difficulty via the left antecubital vein into the right atrium. The patient had to be given oxygen by mask shortly after the procedure started because of increasing cyanosis. Her condition improved and the catheterization was continued. During the procedure, the catheter passed through an interatrial septal defect into the left atrium and then into a left pulmonary vein. The catheter was also passed from the right ventricle into the aorta but never into the pulmonary artery.

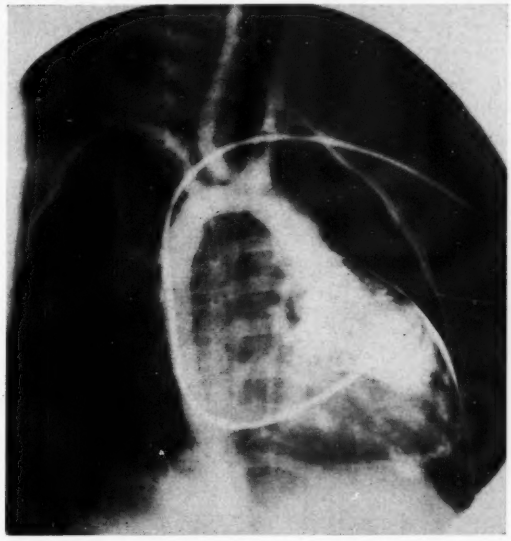

Fig. 1.—Early angiocardiographic film showing contrast material in the pericardial cavity. Note the transposed aorta and failure of pulmonary vessel opacification.

Pressures in the aorta were 58/28 mm. Hg and in the right ventricle 56/5-10 mm. Hg. The catheter tip was then placed deep in the apex of the right ventricle. The diagnostic catheterization itself concluded at 3:00 P.M.

The patient was placed in a slight left posterior oblique position on a Schönander serialographic film changer. A preliminary film showed no change in the location of the catheter tip. The condition of the patient seemed satisfactory with continuous oxygen therapy.

At 3:20 P.M., 8 ml. of 90 per cent Hypaque was injected using a pressure of 10 Kg. per square centimeter. The injection lasted slightly over 2 seconds and was well tolerated. Films were taken at a rate of six per second for 2 seconds followed by four per second for 4 seconds. Continuous electrocardiographic monitoring showed no significant changes. Therefore, the catheter was left in place during the 10 minutes required for developing and viewing of the films. On viewing the films, it was obvious that part of the contrast medium was in the myocardial wall and pericardial cavity. A lateral film was immediately obtained to verify the catheter position and an attempt was made to aspirate the pericardial cavity via the catheter. Less than 2 cm. of dye was obtained, followed by bright red blood. The catheter was carefully withdrawn. Auscultation of the heart by members of the cardiac surgery team present during the injection disclosed a loud pericardial friction rub. The quality of the heart tones, however, seemed unchanged.

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Careful monitoring of the pulse and blood pressure was begun and the operating room alerted. However, the patient's condition remained stable. A chest film 30 minutes after the injection showed some residual dye in the pericardial cavity but no significant change in cardiac size or contour. At 4:45 P.M., the patient was transferred to her room where the constant surveillance was continued. Her vital signs and general condition remained stable.

Chest films the following morning showed complete disappearance of the contrast medium and no change in the cardiac silhouette. An electrocardiogram showed a 2:1 auriculoventricular block but no changes suggestive of pericarditis. The remaining hospital course was uneventful and the patient was discharged from the hospital on Jan. 28, 1959.

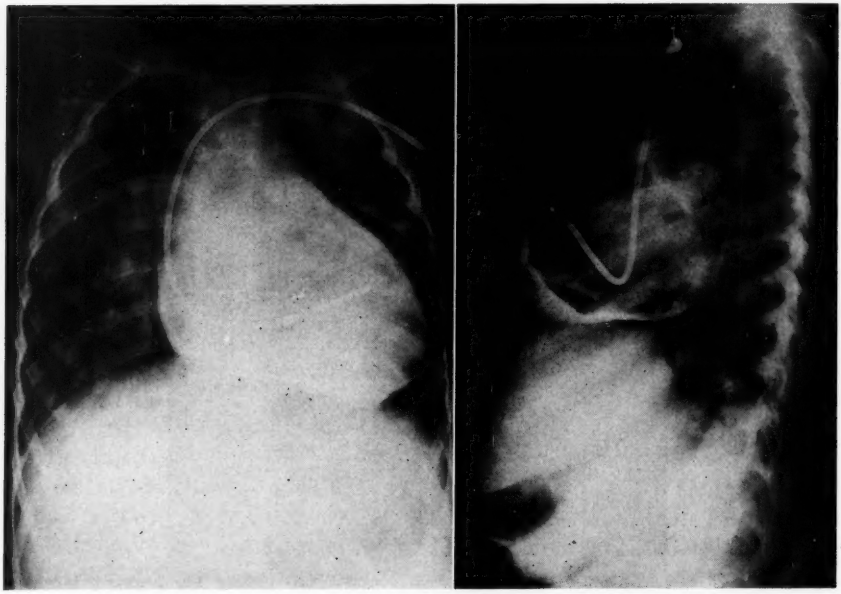

Fig. 2. Fig. 3.

Fig. 2.—Chest film just prior to catheter withdrawal.
Fig. 3.—(Lateral of Fig. 2.) Note residual dye in pericardial cavity.

Angiocardiography confirmed the clinical impression of complete transposition, demonstrating aortic filling from the right ventricle and a right-sided descending aorta. A left innominate artery was also present. At no time was any contrast material seen in the pulmonary vessels.

DISCUSSION

Selective angiocardiography offers definite advantages over venous techniques in the diagnosis of congenital cardiac lesions. Among the latter are the ability to use less contrast medium, precise placement of the contrast agent, and elimination of superimposition. As ordinarily performed, this technique is associated with a minimal morbidity and mortality,[1] in spite of the poor general condition of many of the subjects.

Perforation of the heart is a serious though fortunately rare complication. Using closed-tipped, relatively wide-bored, side-opening catheters, the problem of recoil and high pressure jets encountered with the older Cournand catheters has been partially solved. However, the newer type catheter introduces the difficulty of precise localization with pressure and oxygen determinations because of the multiple holes proximal to its tip. One opening suffices to draw blood samples but the exact localization of the 2 cm. of catheter distal to the most proximal hole can only be inferred from fluoroscopy and film. As Escher and his co-workers[5] have pointed out, the advantages of the N.I.H. catheter justify the risk of its use and certain precautions can be taken to reduce this risk to a minimum.

Blind manipulation of the catheter should be avoided. If necessary, repeat scout films should be taken prior to injection. Hilbish and Morrow[2] have emphasized this in presenting a case in which withdrawal of the catheter 4 inches failed to change the position of the catheter tip in the pulmonary artery. Tightening of the intracardiac loop with no change in position of the distal catheter can only be detected by repeat films or fluoroscopy.

The time during which the catheter remains unchanged in position within the heart should be reduced to a minimum. Subendocardial hemorrhage and mural thrombus formation have been observed in dogs following catheterization[7] but are probably uncommon in human beings. Nonetheless, prolonged delays between positioning and injection increase the risk of endocardial damage.

In our case, the most important factor conducive to perforation is considered to be the position of the catheter. To advance the catheter deep into the apex of the right ventricle places the tip against the junction of septum and ventricular wall. The slight apical elevation accompanying each systole may impale the thin right ventricular apex against the rigid, relatively sharp-tipped N.I.H. catheter. It is easy, under these circumstances, to visualize perforation of the endocardium with insinuation of the catheter between the myocardial fibers. The more energetically the catheter is secured in the right ventricular apex and the longer it is left in this position, the greater the likelihood of this complication. In studying right ventricular outflow tract problems, our current policy is to advance the catheter tip well into the outflow tract so that its course describes the characteristic U-shaped configuration. After positioning, one should be able to freely advance or withdraw the catheter a distance of a few centimeters. If a more proximal injection is desired, for example, to demonstrate an interventricular septal defect, the catheter tip is positioned slightly distal to the atrioventricular valve as determined by pressure readings. Under no circumstances should the catheter be advanced until resistance is met and left deep in the right ventricular apex. Such a technique, especially in the thin-walled right ventricle of infants, entails an additional unnecessary risk. If a satisfactory U-shaped bend cannot be achieved in studying right ventricular outflow problems, the catheter should be withdrawn proximally under fluoroscopic control to a point just distal to the tricuspid valve.

The treatment in this case was wholly expectant. Aspiration through the catheter prior to its removal undoubtedly failed to recover all of the pericardial fluid. Serial chest films are of little value for, as Escher and her colleagues[5] have pointed out, the volume of pericardial fluid producing acute tamponade is close to the minimal amount that can be visualized roentgenographically. Frequent observations of the clinical signs and symptoms provide the best guide to therapy. Should tamponade develop, pericardicentesis or open pericardiotomy may be required. However, many of these patients are poor surgical risks by the very nature of their disease and the conservative therapeutic approach should be given first consideration.

SUMMARY

A case of perforation of the right ventricle during selective angiocardiography has been presented. Possible contributory factors, especially the positioning of the catheter, have been considered. Recommendations are made to help avoid this complication.

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BILATERAL SURGICAL TREATMENT OF PULMONARY TUBERCULOSIS

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SINCE the early optimistic reports,[1-5] bilateral resection for pulmonary tuberculosis has gained considerable acceptance. However, opinions vary regarding the indications, results, and risks of the procedure. With few exceptions, reported series are small and usually include carefully chosen patients with little disease.[6-10] A number of surgeons and phthisiologists believe bilateral pulmonary resection to be less successful than unilateral resection.[12] Greater differences of opinion exist regarding the applicability of procedures such as bilateral thoracoplasty and Monaldi cavernostomy,[13] neither of which has gained popularity.

It is the purpose of this paper to review the experience at the Ray Brook State Tuberculosis Hospital with bilateral surgical procedures, including Monaldi cavernostomy, thoracoplasty, pulmonary decortication, and resection in an attempt to evaluate them.

Since July 1, 1949, 103 patients have completed bilateral surgery. Eighty-three patients had bilateral pulmonary resection, of which 164 were performed at Ray Brook, and 3, prior to admission. Two of the patients had 3 resections each. Four of the patients were admitted to Ray Brook with thoracoplasties. Twenty patients were treated with miscellaneous surgical procedures listed in Table II.

In this series there were 59 males and 44 females. Sex does not seem to be an important consideration in selecting patients for operation; nor does it seem to influence results to an appreciable extent. Ninety-five of the 103 patients in this series, or 94 per cent, were under the age of 50 years at the time of the last surgical procedure. Only 1 patient was over 60 years of age. Age distribution was similar in the bilateral resection and miscellaneous bilateral surgery groups.

BILATERAL PULMONARY RESECTION

The first bilateral pulmonary resection was completed in December, 1951. A total of 164 procedures are summarized in Table I. Two of these were simultaneous. Since bacteriology, extent of disease, antituberculous drug therapy, and type of surgery can be expected to influence results, this information is listed. "New" drugs include pyrazinamide, cycloserine, viomycin, kanamycin,

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TABLE I. BILATERAL PULMONARY RESECTIONS

	NUMBER OF PROCEDURES	EXTENT OF DISEASE*			DRUGS ADMINISTERED AT OPERATION†			OPERATIVE PROCEDURE‡				COMPLICATIONS		
												EARLY		
		MINIMAL	MODERATE	FAR-ADVANCED	SM, PAS, OR INH	"NEW"	NONE	P	L	S	W	TUBERCULOUS	NON-TUBERCULOUS	LATE TUBERCULOUS
Patients harboring culturable tubercle bacilli§	48	1	23	24	18	27	3	1	18	10	19	6	1	4
Patients harboring no culturable tubercle bacilli	116	7	84	25	109	6	1	0	7	26	83	0	2	1
Total	164													

*National Tuberculosis Association classification.

†SM = Streptomycin; PAS = para-aminosalicylic acid; INH = isoniazid.

‡P = Pneumonectomy; L = lobectomy with or without segmental and/or wedge resection; S = segmental with or without wedge resection; W = wedge.

§Resected tissue and/or expectorations.

Promizole, and Tibione. Only drugs to which the patient's organisms proved susceptible are listed. Tubercle bacilli are considered susceptible to streptomycin or para-aminosalicylic acid if they do not grow in the presence of 10 mcg. per milliliter, and to isoniazid if they do not grow in the presence of 5 mcg. per milliliter. Details of susceptibility tests have been described elsewhere.[14] Tubercle bacilli are considered susceptible to the "new" drugs if the patient has not previously received them. Early tuberculous complications include empyema or spread of disease occurring within a period of 1 month following surgery. Nontuberculous complications include hemothorax, nontuberculous empyema, and transient increases in abnormal shadows in the postoperative roentgenogram. Pleural "space problems" are not listed, but an indication of their frequency may be surmised from the fact that 21 postresection thoracoplasties were performed. It should be noted, however, that early in this series some thoracoplasties were performed to prevent overdistention of the residual lung tissue. At present, thoracoplasty is employed only to obliterate residual pleural spaces or empyemas. Late tuberculous complications include reappearance of culturable tubercle bacilli in the expectorations or increase in disease by roentgenogram after the first postoperative month.

From general experience it is to be expected that patients who have extensive disease and harbor culturable tubercle bacilli would have more tuberculous complications than those who do not.[15] Table I shows that there were no early tuberculous complications and only one late bacteriologic relapse in the group of patients who did not harbor culturable tubercle bacilli. In 6 early tuberculous cases, complications occurred in 5 patients who harbored viable bacilli and included 5 empyemas and 1 spread of disease. Two of these patients received no effective drug therapy. Two received "new" drugs and 1 received para-aminosalicylic acid alone. Further surgery in the form of pulmonary resection, decortication and thoracoplasty succeeded in curing 2 patients of their complications. Nontuberculous complications included 2 transient increases in abnormal shadows on the postoperative roentgenogram and 1 staphylococcal empyema. The latter was successfully treated by thoracentesis and antibiotics. The late tuberculous complications included 5 bacteriologic relapses accompanied in 2 instances by changes in chest roentgenogram and in 1 instance by ulceration of the stump of a resected bronchus. Three of the 5 patients who suffered relapses received "new" drugs and 1 refused to take antitubercuious drug therapy after the first postoperative month. Further antituberculous drug therapy succeeded in eliminating tubercle bacilli from the expectorations of 2 of the 3 patients who did not have changes in the chest roentgenogram. One of the other 2 patients responded satisfactorily to additional pulmonary resection. There was only one death, due to "heart failure," which occurred approximately 4 years after the last surgical procedure had been performed. Thus, of the 83 patients, many of whom had advanced disease, 82 are living and 77 (94 per cent) have stable roentgenograms and expectorations free of tubercle bacilli.

As every effort was made to conserve functional lung tissue, it is not surprising that pneumonectomy and lobectomy were performed in only 26 instances. In patients with extensive disease, the surgeon may be forced to limit

TABLE II. MISCELLANEOUS BILATERAL SURGICAL PROCEDURES

PROCEDURES	NUMBER OF PATIENTS	EXTENT OF DISEASE*			PATIENTS HARBORING CULTURABLE TUBERCLE BACILLI		ANTITUBERCULOUS DRUGS AT TIME OF SURGERY		RESULTS		
		MINIMAL	MODERATE	FAR-ADVANCED	YES	NO	YES	NO	STABLE ROENTGENOGRAM AND EXPECTORATIONS FREE OF TUBERCLE BACILLI	UNSTABLE ROENTGENOGRAM OR EXPECTORATIONS CONTAINING TUBERCLE BACILLI	DEAD
Resection + contralateral exploration	1			1	1		1				1
Resection + contralateral Monaldi	2			2	2		2		2		
Resection + contralateral standard thoracoplasty	4†			4	3	1	4		3		1
Bilateral resection + unilateral modified Schede	1‡			1	1		1			1	
Monaldi + standard thoracoplasty + contralateral resection	1§			1	1		1		1		
Resection + decortication + standard thoracoplasty	2		1	1	1	1	2		2		
Resection + decortication + plombage thoracoplasty	1		1			1	1		1		
Bilateral plombage thoracoplasty + resection + contralateral decortication	1			1	1		1				1
Bilateral standard thoracoplasty and unilateral Monaldi	1‖			1	1		1				1
Bilateral plombage thoracoplasty + unilateral Monaldi	1			1	1		1			1	
Bilateral standard thoracoplasty + bilateral Monaldi	2			2	2				1		1
Bilateral standard thoracoplasty	3		1	2	3		1	2	2		1
Total	20										

*National Tuberculosis Association classification.
†Thoracoplasties were performed prior to admission.
‡One resection was performed prior to admission.
§Monaldi and thoracoplasty were performed prior to admission.
‖One thoracoplasty was performed prior to admission.

resection to cavity-bearing tissues, leaving behind considerable amounts of nodular disease. The technical aspects of this problem have been reviewed.[15] Occasionally, it may be impossible to identify pulmonary cavities by either preoperative roentgenogram or palpation at exploration. Under such circumstances, the part of lung suspected of bearing a cavity can be incised without danger. Bleeding from the lung is easily controlled by Allis clamps. Thus, also, cavities can be inspected to determine whether or not they contain purulent material or are lined by a smooth, glistening membrane. The risk from contamination of the pleural cavity is minimal when antituberculous drugs are administered postoperatively.

Because of the unfavorable effect on pulmonary function, thoracoplasty should be avoided whenever possible. Although postresection pleural air spaces should be eliminated without delay in patients harboring viable tubercle bacilli, they may be observed with little risk for considerable periods of time when culturable tubercle bacilli have not been recovered from the sputum or tissues at the time of operation.

In the 80 patients who had both operations performed at Ray Brook, the disease in each lung was equal in 39 patients. In the remaining patients, who had unequally distributed disease, the more diseased lung was operated upon first in 20 instances. Decisions regarding the side to be operated upon first were generally not influenced by the bacteriologic studies of the expectorations, the extent of disease, or antituberculous drugs administered. No difference in results can be demonstrated between the group in which the worst side was operated upon first compared with the group in which the worst side was operated upon last. It would, therefore, seem unimportant which side is chosen for the first operation. The only exception appears to be the patients with a functionless lung who harbor viable tubercle bacilli, since they require extensive space-filling thoracoplasty following pneumonectomy. Since thoracoplasty tends to reduce pulmonary function even if performed over an empty pleural cavity or a functionless lung,[16] it should be performed only after the contralateral resection has been completed and function on that side has recovered to a considerable extent.

In this series, the interval between resections has varied considerably. For several years the second resection has been performed as soon as the patient's vital capacity has recovered sufficiently to tolerate another procedure, other factors being equal. Patients with exceedingly good function may easily tolerate simultaneous bilateral resection, which was accomplished in 1 patient in this series. It has been our experience that following pulmonary resection the vital capacity has recovered to a considerable degree by the sixth postoperative week.[17]

MISCELLANEOUS BILATERAL SURGICAL PROCEDURES

Various combinations of surgical procedures performed upon 20 patients are listed in Table II. These included Monaldi cavernostomy, various types of thoracoplasty, pulmonary decortication, and pulmonary resection. It will be

noted that a proportion of these patients had extensive disease and harbored culturable tubercle bacilli in their expectorations. A number of these patients, too ill for bilateral pulmonary resection, were treated by plombage thoracoplasty and/or Monaldi cavernostomy. Twelve (60 per cent) are now alive with stable roentgenograms and expectorations free of tubercle bacilli. Two patients still have cavitary disease and viable tubercle bacilli in their expectorations. Six (30 per cent) are dead. Two patients died of pulmonary insufficiency within a few weeks following surgery, 1 died of a "heart attack" approximately 3 years after the last operation, 1 died in uremia due to amyloidosis approximately 3 years after pulmonary resection, 1 died of liver toxicity, probably the result of pyrazinamide intoxication, and 1 died a few hours after surgery following cardiac arrest on the operating table. Nonfatal complications in this group of patients consisted of 1 (tuberculous) infected plomb requiring evacuation of foreign bodies, and 1 hemothorax requiring re-exploration.

TABLE III. FUNCTION STUDIES

	NUMBER OF PATIENTS		PREOPERATIVE VITAL CAPACITY		POSTOPERATIVE VITAL CAPACITY (PER CENT PREOPERATIVE VALUE)	
	M	F	M	F	M	F
Bilateral resection + bilateral standard thoracoplasty	1		3,600		2,000* (56%)	
Bilateral standard thoracoplasty	1		4,450		2,260† (59%)	
Bilateral resection + unilateral standard thoracoplasty	4	3	2,360	2,480	1,930‡ (82%)	1,630§ (66%)
Resection + contralateral Schede thoracoplasty		1		1,850		1,300¶ (70%)
Bilateral resection	18	6	3,490	2,520	3,060 (87%)	1,960 (77%)
Resection + contralateral Monaldi	1		3,500		3,200 (92%)	
Monaldi + contralateral decortication + thoracoplasty	1		2,800		2,700‖ (96%)	
Resection + contralateral decortication + plombage		1		1,500		1,600# (107%)
Bilateral plombage thoracoplasty	1	1	1,800	1,300	1,800** (100%)	1,100†† (85%)
Bilateral resection + unilateral decortication	1		2,000		2,450 (123%)	
Totals	28	12				

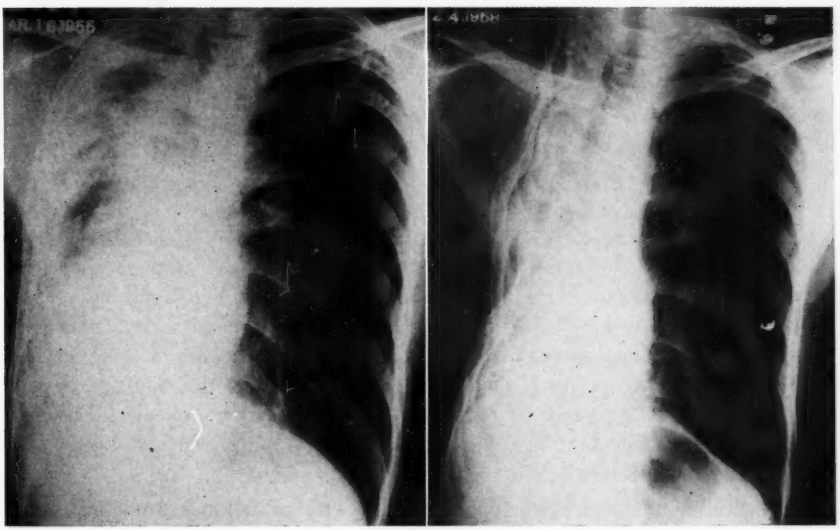
*Five ribs removed bilaterally.
†Bilateral 6-rib thoracoplasty.
‡Nine ribs, 4 ribs, 3 ribs, and 2 ribs removed, respectively.
§Four ribs removed from each of 2 patients and 3 ribs from the other.
¶Four-rib modified Schede thoracoplasty.
‖Four-rib standard thoracoplasty.
#Five ribs.
**Five ribs on one side and 7 on the other.
††Six ribs on one side and 8 ribs on the other.

PULMONARY FUNCTION

Table III summarizes the effects of various combinations of surgical procedures upon the vital capacity. Postoperative determinations were accom-

plished 2 months or more following the last procedure. Undoubtedly the postoperative values might have been somewhat higher if longer periods of time had been permitted to elapse following surgery, but it is believed that 2 months is sufficient time to permit recovery of a major portion of postoperative function.[18] Bilateral plombage thoracoplasty was surprisingly innocuous. Bilateral pulmonary resection was followed by a decrease of approximately 20 per cent in vital capacity. As might have been expected, Monaldi cavernostomy was relatively innocuous; and pulmonary decortication was sometimes followed by improvement in function. These results are similar to those of Gaensler and Strieder.[19]

It is impossible to define the lower limits of pulmonary function which will permit bilateral pulmonary surgery. In borderline cases the decision to do the second operation should be postponed until it is determined that the patient has tolerated the first procedure well. Case 1 is an example of a patient who did well in spite of poor pulmonary function.



A. *B.*

Fig. 1.—*A*, Preoperative roentgenogram revealing destroyed right lung which contains a large cavity with a fluid level. There is cavitary disease in the upper left lung field. *B*, Roentgenogram following bilateral pulmonary resection and right thoracoplasty.

CASE REPORT

CASE 1.—F. T., a 24-year-old man, was admitted to Ray Brook State Tuberculosis Hospital on April 24, 1954, with far-advanced active pulmonary tuberculosis. Known onset of pulmonary disease was December, 1947, when an abnormality in the right lung was noted. He was treated by a rest regimen. In March, 1953, the patient developed fever and productive cough accompanied by fatigue and weight loss. Roentgenograms revealed evidence of extensive disease in the right lung and expectorations contained tubercle bacilli. Streptomycin, isoniazid, and para-aminosalicylic acid were prescribed, but the latter drug was stopped because of fever and rash.

Admission roentgenograms of the chest at Ray Brook (Fig. 1) revealed complete destruction and cavitation of the right lung and evidence of 2 small cavities in the outer first and second anterior interspaces on the left. Tubercle bacilli recovered from the patient's expectorations grew abundantly in 10 mcg. per milliliter of streptomycin and 5 mcg. per milliliter of isoniazid. The patient was gradually desensitized to para-aminosalicylic acid and full dosage of 12 grams a day was reached by Aug. 22, 1954. On March 18, 1955, pyrazinamide, 1 gram 3 times a day, was started. On March 28, 1955, a wedge resection of the cavity-bearing portion of the left lung was performed. The postoperative course was uncomplicated. On June 6, a right pleuropneumonectomy was accomplished. On June 13, it was necessary to do a temporary tracheotomy to maintain the tracheobronchial tree free of secretions. On July 25, a 9-rib right thoracoplasty was performed. Postoperatively the patient did well except for the reappearance of tubercle bacilli in the expectorations of Jan. 25, 1956. Bronchoscopy revealed redness and edema of the stump of the right main bronchus. Expectorations continued intermittently to yield tubercle bacilli. On Nov. 9, 1956, bronchograms failed to reveal evidence of a fistula or pleural pocket connected with the stump of the right main bronchus. On Nov. 17, 1956, pyrazinamide and para-aminosalicylic acid were discontinued and tetracycline, 250 mg. 4 times a day, and cycloserine, 250 mg. twice a day, were substituted. The latter drugs were continued until Jan. 16, 1958. The patient continued to discharge viable tubercle bacilli until Jan. 21, 1957, after which bacilli could not be identified. Tubercle bacilli recovered from the resected right lung grew abundantly in the presence of 10 mcg. per milliliter of para-aminosalicylic acid. Vital capacity on March 7, 1955, was 2,100 c.c. and on March 17, 1958, it was 1,700 c.c.

The patient was discharged from the hospital on March 29, 1958, and until his last examination in October, 1958, had remained well. In May, 1959, he reported he was well and working.

DISCUSSION

A considerable proportion of the tuberculous complications which occurred following bilateral pulmonary resection may be attributed to poor antituberculous drug coverage. Even so, the results were remarkably favorable. These results were undoubtedly influenced by careful selection of patients for surgery. Indeed, perhaps selection was too careful, for a higher incidence of complications would have been acceptable if the benefits of bilateral resection could have been extended to more seriously ill patients. This assumption appears to be substantiated by the fact that the patients in this series with extensive disease who harbored viable tubercle bacilli responded well to surgery.

Generally, bilateral pulmonary resection with or without decortication or a small thoracoplasty offers the best opportunity for cure with relatively little permanent effect upon pulmonary function. However, since open thoracotomy is followed by a severe temporary decrease in pulmonary ventilation postoperatively,[17] it may be preferable to perform plombage thoracoplasty or Monaldi cavernostomy in patients with limited pulmonary function. These technical problems have been reviewed elsewhere.[15]

SUMMARY

One hundred and three patients with pulmonary tuberculosis have been treated by bilateral surgical procedures. The best results were obtained in the group of patients who had bilateral pulmonary resection. Other procedures

yielded good results considering the severity of the tuberculosis and complicating diseases. The effects of various combinations of surgical procedures upon pulmonary function are reviewed.

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EXPERIMENTAL CHRONIC TUBERCULOUS PERICARDITIS

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PREVIOUSLY, we reported the experimental production of tuberculous pericarditis in animals by sensitization with heat killed bacilli followed by the intrapericardial injection of live bovine tubercle organisms. Typical tuberculous pericarditis developed in all animals which survived the immediate postoperative period. The animals were sacrificed at intervals, the longest being 3 months. No constrictive pericarditis was found. In the following study, the animals were kept for longer periods with the hope that the constrictive phase of tuberculous pericarditis would develop. To our knowledge, this has not been accomplished experimentally.

METHOD

Young New Zealand white rabbits were used. Approximately one half of the animals were injected with heat killed tubercle bacilli suspended in Bayol F and were later found to have positive intradermal tests for sensitivity. (Subsequently, it was felt that sensitization was unnecessary as the same degree of pericarditis developed.) Approximately 0.5 c.c. of a milky suspension of live bovine tubercle bacilli was injected into the pericardium after making a small incision in the left fourth or fifth intercostal space. A high postoperative mortality rate occurred in spite of careful wound closure. The animals were isolated but given no special treatment for their tuberculosis. Eighteen animals survived 6 months or longer. One animal died during the seventh month, 3 during the ninth month, and 4 during the tenth month after injection. Because of this increasing mortality, 5 animals were sacrificed during the eleventh month and 5 during the twelfth month. The latter group lacked 3 weeks of living 1 year after injection.

RESULTS

All animals had diffuse tuberculous pericarditis. In those animals sacrificed, after anesthesia had been obtained, the thorax was widely opened to observe the

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heart action and no evidence of constriction was found in any animal. The pericardium was usually slightly thickened and had lost the normal glossy sheen. A small increase in the pericardial fluid was present. Tubercle formation was evident almost uniformly to a greater extent over the epicardium, particularly in the vicinity of the coronary vessels. Tuberculosis was not found elsewhere in the animals, although the brain was not removed.

Microscopically, all stages of the granulomatous process were observed but the main reaction consisted of lymphocyte and macrophage tubercle formation. A few giant cells were seen. In every animal, and in practically every section made, at least one area of calcification was found but this was never large in area nor widespread in extent. Fibrous tissue deposition was also not extensive.

SUMMARY

Chronic tuberculous pericarditis was produced in rabbits by the intrapericardial injection of live bovine tubercle bacilli. Animals surviving from 6 to 12 months showed an extensive granulomatous reaction with areas of calcium deposition but constrictive pericarditis was not produced.

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PRE- AND POSTOPERATIVE CARDIOPULMONARY DYNAMICS OF THE EMPHYSEMATOUS BULLA

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REPORTS on giant emphysematous bullae have become increasingly frequent not only with respect to cases of successful treatment by surgery but also in the number of cases diagnosed roentgenologically.[4, 5, 16, 19, 20, 23, 24, 28, 29, 36] However, reports on the cardiopulmonary dynamics of the disease have been extremely few. Baldwin and her colleagues[6, 7] reported respiratory function in patients with emphysematous bullae with and without emphysema, and Siebens and his associates[32] made a report of cases of bullae without emphysema, but these authors failed to agree in the interpretation of the hypoxia associated with the giant bullae. As for cardiopulmonary dynamics, chiefly of the pulmonary circulation, FitzPatrick[21] reported a number of cases with and without emphysema. With reference to bullae without emphysema, there seems to have been no divergence of opinion as to the indications for operation, operative methods, and the results of physiologic investigation, but in the case of bullae with emphysema there has been confusion, not only as to indications for surgery but also in the results of physiologic investigation.

Out of 11 cases of giant bullae diagnosed by us, 8 patients were surgically treated and this report concerns the pre- and postoperative data of respiratory function and pulmonary circulation, the operative indications, and a more rational approach in the care of giant bullae.

MATERIAL AND METHODS

There were 11 cases of bullae larger than a child's head in size (Table I). In most cases several years had elapsed before any signs developed. Only 2 patients had shown symptoms of anoxia and hypercapnia to the point of incapacitation. Eight patients were operated upon. Segmental resection was usually applied, but in a few cases Naclerio-Langer's operation[25] was performed. After disposal of the bullae, the vagus nerve was divided in its trunk on the right, but when the affected side was on the left, vagotomy was performed in the portion distal to the emergence of the recurrent nerve, with division of its pulmonary branches at the hilus. Furthermore, a sympathectomy of the lung was

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TABLE I. CLINICAL FINDINGS

CASE NO.	AGE	CHIEF COMPLAINTS	OPERATION METHOD	FOLLOW-UP
137	32	Emaciation	Segmental resection, denervation, pleurectomy, and pleural poudrage	Well and enjoying ping-pong
096	57	Bloody sputum, cough and palpitation under exercise		
119	60	Sputum, dyspnea, and palpitation under exercise	Segmental resection, denervation, pleurectomy and pleural poudrage	Better
162	45	Slight fever and emaciation	Segmental resection, denervation, and pleural poudrage	
012	23	Asthma attack, dyspnea, and emaciation	Naclerio-Langer's operation	Asthma attack
188	51	Sputum		
104	61	Cough and dyspnea		
220	43	Cough, sputum, and dyspnea	Segmental resection, denervation, pleurectomy, and pleural poudrage	Better symptomatically
224	52	Cough and sputum	Segmental resection, denervation, pleurectomy, and pleural poudrage	
088	48	Dyspnea, cough, and sputum	Naclerio-Langer's operation; denervation and pleural poudrage	
152	44	Exertional dyspnea and emaciation	Naclerio-Langer's operation; denervation, pleurectomy, and pleural poudrage	Asthma attack

performed by thoracic ganglionectomy (D_2-D_9), and a trial was made of parietal pleurectomy and pleural poudrage in accordance with the technique of Crenshaw and his associates.[11, 12, 13]

All patients were discharged 4 to 8 weeks after the operation, and all were working full time a half year after surgical intervention. Two patients with incapacitating symptoms and signs were greatly improved after the operation and resumed work. The first patient was an exceptional one in whom only Naclerio-Langer's operation had been performed, without denervation and pleural poudrage. Severe asthma developed followed by a relapse 2 years after operation. This was corrected by a second operation 3 years after the first one.

METHODS OF MEASUREMENT

1. *Spirometric Measurements.*—Spirometric measurements were taken of vital capacity (VC), minute volume (MV), the maximum breathing capacity (MBC), and oxygen consumption. Minute volume was recorded as liters per minute per square meter of body surface. Ventilatory equivalent was expressed by air volume to be ventilated due to consumption of 100 c.c. of oxygen as L unit (liters per 100 c.c. of oxygen consumed). VC and MBC were shown as a percentage of their predicted values, which were measured by the method of Baldwin, Richards, and Cournand.[6]

$$\text{Respiratory reserve quotient} = \frac{\text{MBC} - \text{MV}}{\text{MBC}}.$$

$$\text{Air velocity index (AVI)} = \frac{\text{Predicted MBC \%}}{\text{Predicted VC \%}}.^{22}$$

2. *Respiratory Gas Measurement.*—Measurement of residual volume (RV) was made by closed circuit[9] and open circuit methods.[14] Respiratory gas was estimated by using "Roken" gas analysis apparatus (Holden's modified analysis apparatus[37]) or Scholander's gas analyzer.[30]

Total lung capacity (TLC) : RV + VC.
Residual quotient: RV/TLC × 100.

Intrapulmonary gas mixing: nitrogen concentration in the alvéolar air after rebreathing of pure oxygen for 7 minutes.

CO_2 content of alveolar air ($F_{A_{CO_2}}$) : analyzed from endexpiratory samples.

Partial pressure of CO_2 in expiratory gas ($P_{E_{CO_2}}$) and partial pressure of CO_2 in alveolar air ($P_{A_{CO_2}}$) : calculated from CO_2 content in expiratory gas ($F_{E_{CO_2}}$) and CO_2 content in alveolar gas ($F_{A_{CO_2}}$), respectively.

3. *Bronchospirometry.* Measurements were made by using Carlen's flexible double lumen catheter.[8]

Predicted value of the ratio of left to right was shown as the percentage of 46.5/53.5 in VC and of 46.8/53.2 in MBC.

4. *Blood Gas and pH Measurements.*—O_2 and CO_2 contents of arterial blood (Ca_{O_2} and Ca_{CO_2}) were estimated by Van Slyke-Neill's method,[38] and O_2 capacity was measured by Sendroy's method.[31] To estimate the pH of the blood, a glass-electrode[39] was used. Hematocrit (Ht) was measured by using Wintrobe's tube. O_2 saturation of arterial blood (Sa_{O_2}) was calculated from O_2 content and O_2 capacity. Partial pressure of O_2 in arterial blood (Pa_{O_2}), partial pressure of CO_2 in arterial blood (Pa_{CO_2}) and buffer base (Bb′) were computed from O_2 content, CO_2 content, pH of blood, and hematocrit by using Singer-Hasting's nomogram.[34]

5. *Derived Data.*—Oxygen partial pressure difference in millimeters of mercury between "alveolar air" and peripheral arterial blood ($P_{A_{O_2}} - Pa_{O_2}$) and the ratio of alveolar ventilation to pulmonary capillary blood flow ($\dot{V}_A/Qc$) were calculated by the next formula.[10, 26, 28]

$$\frac{\dot{V}_A}{Qc} = \frac{C\bar{v}_{CO_2} - Ca_{CO_2}}{F_{A_{CO_2}} \times 0.83}$$

$C\bar{v}_{CO_2}$: CO_2 content of mixed venous blood.

Dead space ratio: Volume of dead space (VD)/tidal volume (V_T).[10, 26, 28]

$$\frac{VD}{V_T} = \frac{Pa_{CO_2} - P_{E_{CO_2}}}{Pa_{CO_2}}$$

6. *Cardiac Catheterization.*—Both pulmonary arterial pressure and capillary pressure were estimated by an electromanometer, using a cardiac catheter, F. 8. Cardiac output (pulmonary blood flow) and cardiac index were measured by Fick's[18] and dye-dilution[17] methods.

For estimation of pulmonary circulation time, Evans blue dye was used. Arteriovenous O_2 differences were calculated from the O_2 content of arterial and mixed venous blood taken by catheter.

Pulmonary blood volume =

$$\frac{\text{Mean pulmonary circulation time} \times \text{Pulmonary blood flow}}{60}$$ [35]

Ventricular work against pressure =
Cardiac output × Pulmonary mean pressure × 0.1332.[27]

Pulmonary arteriolar resistance =

$$\frac{\text{Pulmonary mean pressure} - \text{Pulmonary capillary pressure}}{\text{Cardiac output}} \times 1332.$$ [15]

Total pulmonary resistance =

$$\frac{\text{Pulmonary mean pressure}}{\text{Cardiac output}} \times 1332.$$

RESULTS

These cases were classified into three groups according to the degree of anoxia and hypercapnia in arterial blood (Baldwin's classification of emphysema).[6]

Group I: Sa_{O_2}: more than 92% (after a standard exercise).
Group II: Sa_{O_2}: less than 92%, Pa_{CO_2}: less than 48 mm. Hg (after a standard exercise).
Group III: Sa_{O_2}: less than 92%, Pa_{CO_2}: more than 48 mm. Hg (after a standard exercise).

1. *Total Lung Capacity.*—When shown as a percentage of the predicted value, VC decreased in the order of the I, II, and III groups (Table II). Residual quotient increased, without relation to the degree of anoxia. TLC decreased even in Group I, and in Groups II and III further steady decrease was noted.

2. *Ventilation.*—Ventilation in liters per minute per square meter of body surface showed no great increase, exclusive of the first case, in which an increase was marked (Table II).

MBC decreased in proportion to the degree of emphysema. Although AVI decreased generally, it showed indefinite values. Respiratory reserve quotient decreased distinctively in Group III.

Although ventilatory equivalent showed indefinite values either at rest or under exercise, it decreased as a rule under exercise.

3. *Bronchospirometry.*—A percentage of its predicted value was expressed as in the ratio 46.5 : 53.5 of left to right. VC decreased on the affected side and MBC also decreased generally on the same side (Table III). MV decreased on the affected side, with one exception. O_2 consumption tended to lessen, except in 2 cases.

TABLE II

		GROUP										
		I		II							III	
CASE NO.		137	096	119	162	012	188	104	220	224	088	152
AGE (YEARS)		32	57	60	45	22	43	57	43	52	48	44
HEIGHT (CM.)		179	169	164	164	165	168	167	163	145	159	159
WEIGHT (Kg.)		53	52	41	55	44	45	51	57	43	44	44
SEX		M	M	M	M	M	M	M	M	M	M	M
Lung Volume												
Vital capacity (%)	B*	93	91	75	117	59	62	77	77	79	38	39
	A†	86	–	58	54	84	–	–	63	54	74	52
RV (%)	B	131	135	136	190	–	147	132	149	143	138	137
	A	245	–	217	158	210	–	–	143	199	201	282
TLC (%)	B	102	110	93	136	–	92	98	95	95	63	84
	A	123	–	108	80	115	–	–	84	90	106	110
$\frac{RV}{TLC} \times 100$	B	32	38	43	35	–	50	41	39	38	54	64
	A	47	–	62	49	45	–	–	45	55	47	64
Ventilation												
VE (L./min./M.²)	B	6.8	4.3	3.8	3.7	–	4.1	3.9	5.4	4.7	4.5	5.1
	A	5.0	–	4.7	3.4	–	–	–	–	–	4.8	4.3
MBC (%)	B	90	76	50	68	22	54	85	81	77	36	24
	A	41	–	49	66	58	–	–	79	41	35	46
AVI	B	0.98	0.84	0.68	0.58	0.37	0.87	1.10	1.05	0.97	0.95	0.62
	A	0.48	–	0.85	1.22	0.69	–	–	1.25	0.77	0.49	0.88
RRQ‡ (%)	B	79	82	62	79	–	80	82	82	82	40	54
	A	66	–	79	85	88	–	–	85	73	50	68
VE§ Rest	B	4.8	3.6	4.5	2.9	–	2.3	4.2	4.0	3.2	2.9	3.3
	A	4.1	–	4.2	3.4	3.5	–	–	3.7	3.8	3.4	3.6
O_2	B	3.3	3.3	2.8	2.6	–	2.7	1.0	2.3	2.8	8.5	2.0
	A	4.2	–	1.7	2.1	1.5	–	–	3.3	3.9	3.3	2.0

*B = Before operation.
†A = After operation.
‡RRQ = Respiratory reserve quotient.
§VE = Respiratory equivalent.

TABLE III. BRONCHOSPIROMETRY

		GROUP															
		I		II										III			
CASE NO.		137		119		162		012		220		224		088		152	
AFFECTED SIDE (IN PARENS.)		r	(l)	(r)	l	(r)	l	(r)	l	(r)	l	r	(l)	(r)	l	(r)	l
VC (%)	B*	69.5	71.4	61.1	87.5	100.0	105.0	45.4	75.0	65.0	94.1	72.2	66.6	23.8	64.7	21.1	52.9
	A†	–	–	83.3	87.5	116.0	105.0	81.8	75.0	75.0	94.0	72.2	73.3	76.1	64.1	52.6	52.9
$\dot{V}_E$ (L./min.)	B	6.0	5.6	3.9	4.6	10.7	7.7	3.9	5.2	4.4	6.2	3.9	3.5	4.0	4.9	2.1	4.9
	A	–	–	5.6	5.9	10.7	7.7	6.8	8.2	5.6	6.4	4.4	3.9	8.6	3.3	5.0	3.3
MBC (%)	B	52.0	55.8	43.8	50.6	55.2	66.9	19.6	25.3	45.6	79.6	42.4	53.7	13.9	20.2	16.5	48.5
	A	–	–	51.8	51.2	62.4	66.9	38.4	42.2	51.2	79.3	43.6	57.8	68.1	56.9	28.4	30.7
$\dot{V}_{O_2}$ (c.c.)	B	460	390	132	287	132	332	250	370	210	110	196	130	110	201	190	220
	A	–	–	272	322	150	224	286	260	250	129	220	210	293	293	224	177

*B = Before operation.
†A = After operation.

TABLE IV

		GROUP																					
		I				II												III					
CASE NO.		096	137			012	104	119			162			188	224		220		088			152		
BEFORE-AFTER OPERATION		B*	B	2M†	10M	B	B	B	2M	9M	B	1M	6M	B	B	2M	B	2M	B	1M	4M	B	1M	6M
Sa_{O_2} (%)	Room air	93	93	94	95	94	87	92	93	94	90	95	95	89	89	91	89	93	84	91	92	86	94	94
	O_2	–	97	97	98	–	–	95	98	98	94	98	96	93	96	95	98	99	97	96	98	93	97	98
Pa_{O_2} (mm. Hg)	Room air	75	73	73	83	–	57	66	71	74	64	79	81	62	60	66	59	72	48	65	68	60	76	78
	O_2	–	116	115	119	–	–	81	113	131	77	109	91	74	98	79	126	137	100	93	123	76	103	113
Pa_{CO_2} (mm. Hg)	Room air	36	36	40	35	48	44	34	36	37	41	37	39	40	44	35	48	44	50	48	42	52	39	40
	O_2	–	36	41	36	–	–	35	39	40	41	39	38	40	44	36	48	44	49	52	45	49	43	38
pH (7.0)	Room air	.48	.38	.41	.40	–	.41	.43	.42	.40	.43	.42	.38	.38	.40	.40	.41	.40	.43	.39	.43	.37	.42	.41
	O_2	–	.38	.40	.39	–	–	.43	.40	.40	.38	.42	.38	.38	.40	.41	.40	.40	.43	.38	.41	.36	.39	.40
Bb (mEq. /L.)	Room air	44	44	46	44	–	49	47	45	45	45	45	46	44	51	42	48	49	53	49	50	45	48	46
	O_2	–	42	49	43	–	–	48	46	46	46	47	42	44	51	44	48	45	53	50	49	47	46	44
HCO_3^- (mEq. /L.)	Room air	22	21	24	21	–	27	23	23	24	24	23	22	24	29	21	27	27	31	28	28	26	25	25
	O_2	–	21	25	21	–	–	24	24	24	24	24	22	24	29	22	27	26	31	29	28	27	26	23

*B = Before operation.
†M = Months after operation.

4. *Index of Intrapulmonary Gas-Mixing.*—It has increased in all cases, but without relation to the degree of emphysema.

5. *Arterial Blood.*—Sa_{O_2} at rest decreased in the order of the I, II, and III groups (Table IV). Improvement was seen, much more so than at 100 per cent O_2 breathing, but never reached 100 per cent in all cases. Pa_{O_2} at rest decreased definitely, but it increased much more than that of 100 per cent O_2 breathing time along with an increase of Sa_{O_2}. Pa_{CO_2} was within the normal limits exclusive of that in Group III and it was not found to be increased more than the time of 100 per cent O_2 breathing. pH was within the normal limits, and Bb′ and HCO_3^- were above the normal value.

6. *Influence of Exercise.*—Minute volume per square meter of body surface increased 2 to 3 times under exercise (Table V). However, ventilatory equivalent decreased under exercise in most cases, although less marked. Sa_{O_2} and Pa_{O_2} tended to decrease under exercise in all cases except 1, and showed no improvement even after 10 minutes. Pa_{CO_2} showed increase under exercise in 6 cases, but decreased in 3 cases, and in most cases recovery took place after 10 minutes, although there was one exception in Group III in which there was no change. pH decreased under exercise in all cases, except 1 in Group III in which there was a return to the value at rest after 30 minutes. Bb′ decreased under exercise in all cases as well as pH, but failed to return to the value at rest even after 10 minutes.

7. *Derived Data* (Table VI).—The physiologic dead space ratio increased. $P_{A_{O_2}} - Pa_{O_2}$ increased more than the normal value in all instances, while $\dot{V}_A/\dot{Q}c$ in most cases showed more than the normal value (0.8), namely, distribution-perfusion-relationship was abnormal.

8. *Pulmonary Circulation.*—Pulmonary arterial pressure rose more than the normal value in all cases as shown in Table VII, especially in 2 cases in Group III. Pulmonary capillary pressure was within the normal limits. Pulmonary blood flow, cardiac index, and stroke volume decreased distinctively in all cases. Arteriovenous difference of O_2 content decreased markedly more than the normal value. Pulmonary arterial resistance and total pulmonary resistance increased in general. Ventricular work against pressure decreased less than the normal value in all cases. Pulmonary blood volume decreased generally less than the normal value with a few exceptions. Mean pulmonary circulation time was prolonged longer than the normal value.

Re-examination of the postoperative cardiopulmonary dynamics 4 to 6 months later revealed the following results.

Postoperative Changes.—VC was decreased by thoracotomy in those patients who had presented normal values, but it increased in a case in Group III, in which there had been a marked decrease before operation. The residual quotient increased in most instances.

There were a number of cases in which TLC increased postoperatively although it had been decreased before the operation. This was particularly true

TABLE V

		GROUP																							
		I				II														III					
CASE NO.		96	137			12	104	119			162			188	220		224			88			152		
BEFORE-AFTER OPERATION		B*	B	2M†	10M	B	B	B	2M	9M	B	1M	6M	B	B	2M	B	2M		B	1M	4M	B	1M	6M
VE (L./min./M.)	Rest	4.8	6.8	5.0	5.1	–	3.9	3.8	4.7	3.7	3.7	4.5	3.4	4.1	5.4	–	4.7	–		4.4	5.7	4.8	5.1	5.5	4.3
	Exercise	12.0	12.8	23.2	14.0	–	14.3	11.7	13.0	12.7	13.7	–	9.5	11.8	–	–	9.8	–		7.9	10.3	11.1	14.5	12.1	10.7
VE‡	Rest	3.6	4.8	–	–	–	4.2	4.5	–	–	2.9	–	–	2.3	4.0	–	3.2	–		2.9	–	–	3.3	–	–
	Exercise	2.7	2.1	–	–	–	3.4	–	–	–	2.5	–	–	1.8	–	–	3.5	–		2.5	–	–	2.2	–	–
Sa_{O_2} %	Rest	93	93	94	95	94	87	92	93	94	90	95	95	89	89	93	89	91		84	91	92	86	94	96
	Exercise	–	88	87	89	–	82	83	87	86	82	95	89	90	80	84	87	91		72	83	78	80	75	89
	10 min. after ex.	–	96	92	89	–	86	85	82	96	77	92	92	88	82	84	87	91		75	83	91	72	88	93
Pa_{O_2} (mm. Hg)	Rest	75	73	73	83	–	57	66	69	74	64	79	81	62	59	72	60	66		48	65	68	86	94	96
	Exercise	–	65	56	62	–	49	51	59	55	49	82	59	68	46	50	57	73		41	49	46	80	75	89
	10 min. after ex.	–	55	58	63	–	54	52	47	59	41	71	62	60	48	50	57	69		45	44	66	72	88	93
Pa_{CO_2} (mm. Hg)	Rest	36	36	40	35	48	44	45	36	50	49	40	45	40	48	44	44	35		50	48	42	52	39	40
	Exercise	–	41	36	33	–	47	38	46	46	43	46	45	43	51	40	45	42		68	47	50	45	35	40
	10 min. after ex.	–	39	43	35	–	43	42	45	47	44	48	44	39	49	41	44	43		65	40	47	44	35	38
pH	Rest	7.40	7.38	7.41	7.40	–	7.41	7.43	7.42	7.40	7.43	7.38	7.38	7.38	7.41	7.40	7.40	7.40		7.43	7.39	7.43	7.37	7.43	7.41
	Exercise	–	7.28	7.39	7.39	–	7.35	7.35	7.32	7.38	7.37	7.40	7.40	7.33	7.38	7.39	7.38	7.31		7.26	7.38	7.35	7.35	7.42	7.36
	10 min. after ex.	–	7.38	7.38	7.39	–	7.39	7.39	7.39	7.43	7.42	7.41	7.41	7.37	7.39	7.39	7.39	7.35		7.25	7.45	7.37	7.40	7.44	7.39
Bb (mEq./L.)	Rest	44	44	46	44	–	49	47	45	46	45	46	43	44	48	49	51	42		53	48	50	45	48	46
	Exercise	–	39	44	42	–	46	42	42	43	42	44	43	42	47	46	51	40		47	48	48	45	45	43
	10 min. after ex.	–	43	47	43	–	49	45	43	45	44	46	43	43	47	47	50	42		47	50	46	45	45	44

*B = Before operation.
†M = Months after operation.
‡VE = Ventilatory equivalent.

TABLE VI

	GROUP																							
	I				II														III					
CASE NO.	137			96	119			162			12	188	104	220		224		088			152		
BEFORE—AFTER OPERATION	2M	B*	10M†	B	B	2M	9M	B	1M	6M	B	B	B	B	2M	B	2M	B	1M	4M	B	1M	6M
VD/VT (%)	35	44	37	44	42	44	32	42	44	32	42	37	41	39	32	49	30	44	44	43	43	43	34
P_{A_0}—Pa_0 (mm. Hg)	29	25	15	23	33	30	25	33	23	6	38	36	40	36	27	37	31	47	31	32	37	22	11
$\dot{V}_A/Qc$	1.2	0.9	—	—	1.0	1.0	—	0.8	0.8	—	—	1.0	1.0	1.1	1.0	1.2	1.0	1.6	1.3	—	1.2	1.1	—

*B = Before operation.
†M = Months after operation.

TABLE VII

	GROUP											
	I		II						III			
CASE NO.	137		119		162		224		088		152	
BEFORE-AFTER OPERATION	B*	A†	B	A	B	A	B	A	B	A	B	A
Pulmonary artery pressure (mm. Hg)												
Systolic	22	27	24	25	22	15	32	27	45	38	30	31
Diastolic	10	6	11	5	10	5	18	12	17	12	17	7
Mean	17	16	16	13	15	10	23	17	26	20	20	17
Pulmonary capillary pressure (mm. Hg)	12	8	11	4	6	5	7	8	5	12	7	5
Cardiac output (L./min.)	3.08	3.81	2.76	4.16	2.54	3.07	2.90	3.60	3.87	7.55	2.67	3.20
Cardiac index (L./min./M.^{2})	1.82	2.32	1.97	2.96	1.59	2.04	1.92	2.38	2.67	5.29	1.88	2.28
Stroke volume (c.c./beat)	46	50	46	55	50	40	44	54	46	100	44	70
O_2 content of arterial blood (vol. %)	19.14	18.75	16.78	13.91	16.79	18.67	21.38	19.48	17.38	14.73	13.01	12.46
O_2 saturation of arterial blood (%)	93.35	94.08	89.86	93.02	89.17	88.95	96.69	95.56	87.30	91.26	86.80	83.09
A-V difference of O_2 content (vol. %)	4.51	5.70	4.32	2.60	3.48	3.11	6.34	4.33	5.65	4.25	3.08	2.87
O_2 consumption (c.c./min.)	139	157	116	108	88	95	184	228	218	321	82	123
Pulmonary arteriolar resistance (dyne/sec./cm.$^{-5}$)	181	235	144	172	285	130	444	199	437	190	423	294
Total pulmonary resistance (dyne/sec./cm.$^{-5}$)	441	335	462	249	432	261	638	377	542	312	597	416
Right ventricular work (jouls/min.)	6.7	6.5	5.7	12.5	4.6	5.6	8.9	8.1	13.1	28.1	6.7	7.2
Pulmonary blood volume (c.c.)	616	825	586	694	509	716	531	651	1032	1636	624	586
Mean pulmonary circulation time (sec.)	12.2	13.4	16.2	10.4	12.7	14.7	11.0	9.4	16.7	10.3	14.3	11.6

*B = Before operation.
†A = After operation.

with the patients in Group III, who had a marked reduction preoperatively. Tidal volume was decreased in 1 patient, who once had shown an increase before operation, but the others showed no change. Although MBC, which had shown a marked preoperative decrease, increased in a few cases, in the majority there was a decrease after thoracotomy. The respiratory reserve quotient was increased in a number of cases, especially in those cases in which it had been low before the operation. Although, ventilatory equivalent was decreased in those cases in which there had been an increase before the operation, it was increased in those cases in which it had been decreased prior to the operation. Oxygen consumption was decreased in those cases which were above normal before the operation, but it had a tendency to increase in those cases which had been lower than normal.

Although intrapulmonary gas mixing was increased before the operation in all cases, it showed the normal value after the operation in most cases. Sa_{O_2} was improved in all cases, especially noticeable in those in which anoxia had been marked before the operation. Improvement of Pa_{O_2} was readily observed, even longer than 2 to 3 months. Pa_{CO_2} showed an indefinite value in those cases which had been within the normal limits, but it apparently decreased and indicated the normal value in those cases (No. 220, 88, and 152), in which there had been higher than normal values.

$P_{A_{O_2}} - Pa_{O_2}$ decreased gradually in all cases after the operation. V_D/V_T decreased in the cases in which there had been a marked increase. $\dot{V}_A/\dot{Q}c$ decreased, getting near the normal value, i.e., 0.8, in all cases in which there had been an increase before the operation.

Postoperative measurement made 4 to 6 months afterward showed definite improvement of pulmonary arterial pressure which came close to the normal value. Pulmonary blood flow and cardiac index became higher. Arteriovenous O_2 difference and pulmonary arteriolar resistance, as well as total pulmonary resistance, decreased together, approaching the normal value. Ventricular work against pressure had a tendency to increase. There were a number of cases in which pulmonary circulation time decreased and returned to normal. Pulmonary blood volume increased generally, approaching the normal value.

DISCUSSION

Giant bullae with poor bronchial-bullous communication by their very nature cause considerable change in the capacity or ventilation of the lung, as shown by Baldwin,[6, 7] and Siebens,[32] and by us. This influence was further demonstrated by a return to normal respiratory function following removal of the bullae.

Although Baldwin[7] stated that hypoxemia which occurs with bullae was due to emphysema of the remaining lung, Siebens[32] reasoned that hypoxia was due to imbalance of alveolar ventilation and capillary blood flow to the remaining lung, which was affirmed by our results. However, as Baldwin and Siebens

mentioned, in cases complicated with hypoxia and hypercapnia, emphysema of the remaining lung may be the cause, which was confirmed by macroscopic findings of the lung at the time of surgery and biopsy.

Bullae seem to create a marked influence on the pulmonary circulation, as evidenced by decreased pulmonary blood flow, increased total pulmonary resistance, and pulmonary hypertension.

Our findings have been shown to be identical with those reported by FitzPatrick,[21] except for pulmonary blood flow.

Our animal experiments[33] have logically shown that altered pulmonary circulation does occur not only in the presence of the bullae but also in the presence of a balloon inserted into the pleural cavity of the animal, or in clinical conditions following extrapleural pneumothorax. It is assumed that functional alteration develops whenever any pressure is exerted on the pulmonary tissue.

The fact that the resection of bullae relieves the characteristic physiologic cardiopulmonary change was well substantiated by our experimental and clinical results which agree with other reports.

When, however, an advanced pulmonary emphysema accompanied the bullae formation, the situation is far more complicated. It is most probable that the return of normal cardiopulmonary dynamics would be least expected despite resection of bullae. Theoretically, the emphysematous condition would continue to exist.

FitzPatrick reported that in the cases in which bullae were removed with poudrage there failed to be improvement in pulmonary arterial hypertension and total pulmonary resistance in certain instances. Besides, hypoxia was not always improved.

Since these results are to be expected, the rational treatment should be resection of the bullae with surgical treatment of the involved emphysema. Crenshaw[11, 12, 13] and Abbott[1, 2, 3] have devised methods for the operative treatment of emphysema, which were aimed at pulmonary denervation with certain variations.

According to his reports, Abbott[1, 2, 3] succeeded in obtaining improvement in symptoms and signs, and in lowering pulmonary arterial hypertension, while Crenshaw[11, 12, 13] was successful in relieving symptoms of advanced emphysematous patients who stood the operation well. Postoperative improvement was definitely observed.

The authors have attempted to resect bullae with incorporation of Crenshaw's operation in the cases in which hypoxemia and hypercapnia were present. These patients improved despite a stormy postoperative course, and eventual remission occurred without fail as attested by lowering pulmonary arterial hypertension, with decreased total pulmonary resistance, thus differing from FitzPatrick's report. The ratio between alveolar ventilation and pulmonary capillary blood flow became normal with correction of hypoxia and absence of hypercapnia.

Baldwin[6, 7] and Siebens,[32] on the contrary, believed that the pulmonary bullae with advanced emphysematous complication should be retained, and that surgical intervention is contraindicated, because of the pulmonary physiology, and because respiratory insufficiency may ensue postoperatively.

Nevertheless, from our experience, emphysema, although advanced, should not necessarily be regarded as a contraindication, for various physiologic tests made after surgery have sufficiently proved the surgery to be legitimate. Therefore, the procedure of choice should be resection of the bullae with denervation for better cardiopulmonary dynamics with relief of symptoms and signs.

SUMMARY

Experiences with 11 cases of giant bullae are reported, in 8 of which resection and denervation were performed, resulting in definite postoperative improvement of symptoms and signs. The results obtained in pre- and postoperative physiologic investigation of the cardiopulmonary functions were:

1. Vital capacity was decreased markedly and residual volume was increased in the cases in which hypercapnia had been present. Gas mixing showed abnormal values in all cases. By means of bronchospirometry, vital capacity, minute volume, the maximum breathing capacity, and oxygen consumption were shown to be decreased on the affected side.

Sa_{O_2} and Pa_{O_2} were decreased, but Pa_{CO_2} increased in Group III. Physiologic dead space ratio and $P_{A_{O_2}} - Pa_{O_2}$ were all increased, but there was definite decrease of pulmonary blood flow and cardiac index. Total pulmonary resistance was increased and pulmonary circulation time was prolonged.

2. Postoperatively, total lung capacity, gas mixing, Sa_{O_2}, Pa_{O_2}, $P_{A_{O_2}} - Pa_{O_2}$, $\dot{V}_A/\dot{Q}c$, pulmonary arterial pressure, pulmonary blood flow, total pulmonary resistance, and circulation time returned to normal values, respectively.

3. Since the abnormal physiologic cardiopulmonary findings in the presence of giant bullae are chiefly due to compression of the bullae on the remaining lung, operation is not contraindicated even if hypoxia is present.

Even in the cases in which giant bullae are complicated with emphysema and in which anoxia, hypercapnia, and pulmonary hypertension are present, normal pulmonary function can be obtained with surgical excision of the bullae, combined with denervation. In our opinion operation is not contraindicated in cases complicated with emphysema, but resection of the bullae with denervation is indicated.

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BRONCHOPULMONARY SEQUESTRATION

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BRONCHOPULMONARY SEQUESTRATION, at one time a subject of importance to anatomists and embryologists alone, has within recent years aroused the interest of thoracic surgeons. The lesion is characterized by two essential features, the cystic or bronchiectatic pulmonary disease and the systemic pulmonary artery supplying the diseased lung. Thus its importance to the thoracic surgeon is of necessity twofold. He is concerned with the preoperative diagnosis of the pulmonary lesion although it is usually only suspected rather than diagnosed. More important, however, is his concern with the operative recognition of the potentially dangerous vascular anomaly.

We have seen 7 patients with this anomaly at the State University of Iowa Hospitals in the past 5 years. Six of these were treated surgically and the seventh was discovered at the postmortem examination of a newborn infant.

PATHOLOGY

The pulmonary lesion is usually one of cystic or bronchiectatic disease of the lower lobe. More often than not the ectopic or sequestrated lung has no communication with the bronchial tree. Commonly, however, the adjacent basilar segments show bronchiectatic changes although they receive no anomalous blood supply. The lesions are usually on the left side and in our series were exclusively so. The cysts may be thin-walled, lined with cuboidal epithelium, or may resemble bronchiogenic cysts with pseudostratified columnar epithelial lining. The anomalous artery ordinarily arises from the lower thoracic aorta but may originate from the abdominal aorta or other abdominal arteries and traverse the diaphragm to reach the sequestrum.[4]

A distinction should be made between intralobar sequestration and extralobar sequestration (accessory lobe). The intralobar sequestrum is embedded in the lower lobe, usually in its posteromedial aspect and characteristically has venous drainage to the pulmonary vein. There is almost invariably an important element of infection. Accessory lobes are entirely separate from the lower lobe and may even be found beneath the diaphragm. There is little doubt, however, that this distinction between the two types may be made virtually impossible by the presence of chronic inflammatory changes binding the accessory lobe

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to surrounding normal lung. Venous drainage from accessory lobes is usually to the hemiazygos vein. Diaphragmatic defects are frequently associated with extralobar sequestration.[1, 3, 4, 12]

CLINICAL FINDINGS

Patients with this condition usually present themselves with histories of recurrent pulmonary infections. In the 8 cases reported by Pryce,[9] 7 of the patients had the onset of symptoms before they were 20 years of age. Our patients experienced a somewhat later onset of symptoms and 3 of the 7 had no symptoms referable to the pulmonary disease. Bronchoscopic examination is apt to show bronchial inflammation and purulent exudate in the lower lobe bronchus. Radiographic findings are not specific but recurrent inflammatory processes, cysts, or bronchiectasis limited to the left lower lobe should make one highly suspicious of pulmonary sequestration. We have not felt the need for angiographic proof of the diagnosis as proposed by Gerard and Lyons.[6]

ETIOLOGY

The cause of this peculiar combination of findings is still in doubt, although numerous theories have been advanced. The issue is clouded by the occurrence of each of the components (systemic pulmonary artery, cystic or bronchiectatic lung disease and, sometimes, diaphragmatic defects) separately.[3] It is nevertheless tempting to postulate some causal linkage between them when they do occur together. Pryce's[8, 9] approach to the problem, set forth so cogently in 1946 and 1947, has found many adherents and is probably the most widely quoted if not the most widely believed of all the applicable theories. Pryce believes that the systemic pulmonary artery, persisting in its fetal attachment to a portion of the lung, causes the "captured" bronchial bud to separate from the main pulmonary mass. This condition of ectopia is then apt to give rise to the pulmonary changes described previously.

R. A. Smith[10] states that an anomalous pulmonary artery is the primary lesion but suspects that the pulmonary changes are secondary to exposure to the relatively high systemic blood pressures.

Berman,[1] among others, believes that the pulmonary anomaly is primary and that the abnormal lung then attracts local independent blood supply from the most available source. Thus, structures having the characteristics of bronchogenic cysts, when they occur at the hilar level or above, are apt to have an independent blood supply from the pulmonary artery while similar structures near the medial aspects of the lower lobes are apt to be supplied by arteries arising from the nearby aorta.

Gebauer[5] carries this thought even further, stating that the primary pulmonary disease, usually acquired, stimulates the hypertrophy of vessels belonging to the "network of the bronchial and mediastinal arteries" and thereby takes the disease almost entirely out of the congenital class.

Boyden,[2] after carefully examining the theories of Pryce and Smith, concludes that "a hypothesis of coincidental occurrence of these anomalies in certain patients is still all that can be warranted by the facts at our disposal."

TREATMENT

Treatment consists of surgical excision of the diseased lung. In cases of extralobar sequestration, the sequestrum alone can be removed. If the sequestration is of the intralobar type, a lobectomy or segmental resection of the basilar segments is usually required. Any accompanying diaphragmatic defect should be repaired. Operative recognition of the lesion and its anomalous blood supply is essential. The systemic pulmonary artery, usually found in the inferior pulmonary ligament, must be carefully dissected out and ligated. Inadvertent cutting or tearing of this vessel may result in serious or even lethal hemorrhage.[7, 11]

CASE REPORTS

Summaries of the cases treated follow. Some of the salient features are presented more succinctly in Table I.

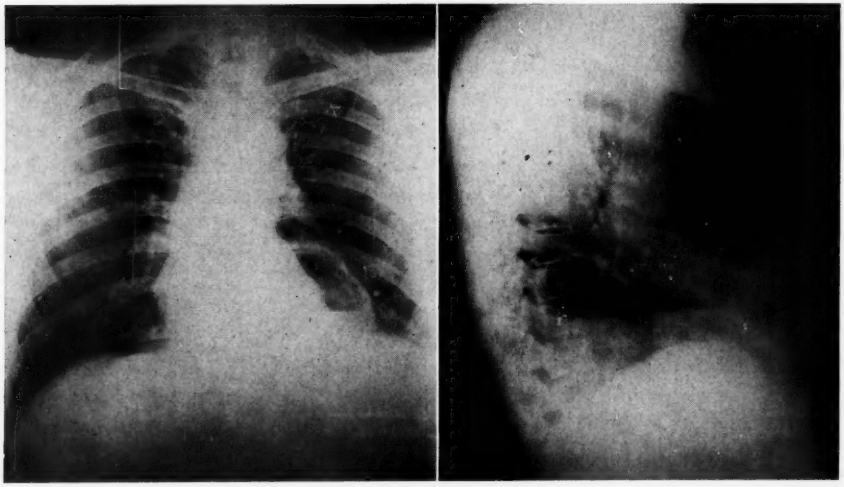
TABLE I

PATIENT	SEX	AGE	DURATION OF SYMPTOMS	BLOOD SUPPLY	INTRA- OR EXTRA-LOBAR	PATHOLOGY	BRONCHIAL COMMUNICATION
1. J. B. S.	M	64	None	Through diaphragm	Extra	Pulmonary congestion and collapse; eventration of diaphragm	None
2. H. B.	M	32	1 yr.	Aorta, 2 vessels	Intra	Advanced chronic inflammation	None
3. C. W.	M	56	2 yr.	Aorta, 3 vessels	Intra	6 cm. cyst and surrounding bronchiectasis	Yes
4. W. C. B.	M	29	None	Aorta, 1 vessel	Intra	Cyst lined with bronchial epithelium; cellulitis of adjacent lung	None
5. R. H.	M	4	1 yr.	Aorta, 1 vessel	Intra	Bronchiectasis and abscesses in basilar segments	Yes
6. D. E.	M	1 day	1 day	Aorta, 1 vessel	Extra	Atelectatic pulmonary tissue with fibrin in alevoli	No
7. L. W.	M	18	6 mo.	Aorta, 1 vessel and pulmonary artery	Intra	Pneumonitis posterior basilar segment	No

CASE 1.—J. B. S., a 64-year-old white man, had no pulmonary symptoms but knew of a "lung cyst" demonstrated in chest roentgenograms 20 years previously. He entered the hospital for treatment of an ulcer. Radiographs revealed a radiolucent area in the left lower chest thought to be a lung cyst or a Bochdalek type diaphragmatic hernia (Fig. 1, *A* and *B*). At surgery, a definite posterolateral diaphragmatic weakness was found. There was also an extralobar sequestration which was removed and which showed congestion and pulmonary collapse microscopically. The blood supply came through the diaphragm from a systemic artery.

CASE 2.—H. B., a 32-year-old white man, had had two episodes of pneumonia in the previous year. Productive cough and dyspnea had followed the second of these which had occurred 6 months previously. Roentgenograms showed an irregular mass in the left lower lobe and bronchograms revealed minimal bronchiectasis of the basilar segments (Fig. 2, *A*, *B*, and *C*). Bronchoscopy showed purulent material coming from the left lower lobe. At the time of surgery an intralobar sequestrum showing advanced chronic inflammation was removed. Its blood supply consisted of two vessels arising from the lower thoracic aorta.

CASE 3.—C. W., a 56-year-old white man, had had pneumonia on the left side 2 years previously and had noticed a chronic cough since then. Roentgenograms of the chest revealed a cyst in the left lower lobe and bronchograms showed basilar bronchiectasis. A lower lobectomy was performed. Three arteries arising from the aorta supplied the cyst. The cyst had a bronchial communication and was lined with pseudostratified columnar epithelium.



A. *B.*

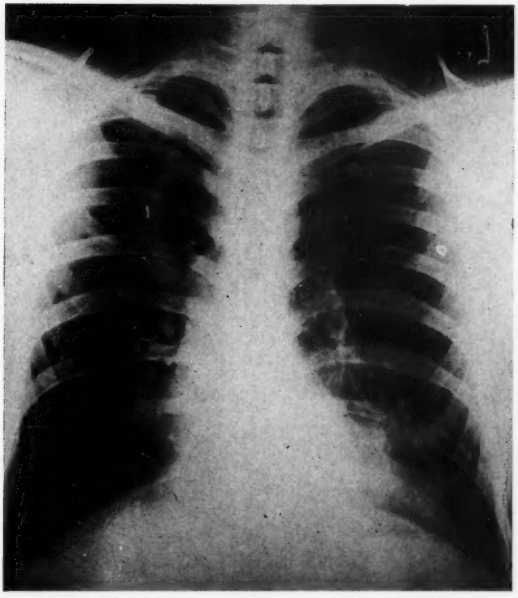
Fig. 1.—(Case 1.) *A* and *B*, Roentgenograms of the chest demonstrating the posterior diaphragmatic defect associated with the extrapulmonary sequestration.

CASE 4.—W. C. B., a 29-year-old white man, had no pulmonary symptoms but a left pulmonary shadow had been noted radiographically 1 month prior to admission. Bronchograms were normal as was bronchoscopy. A lower lobectomy was performed for a 7 cm. mass located posteriorly in the lower lobe. This mass was supplied by one artery coming from the aorta. It was lined with bronchial epithelium although there was no bronchial communication.

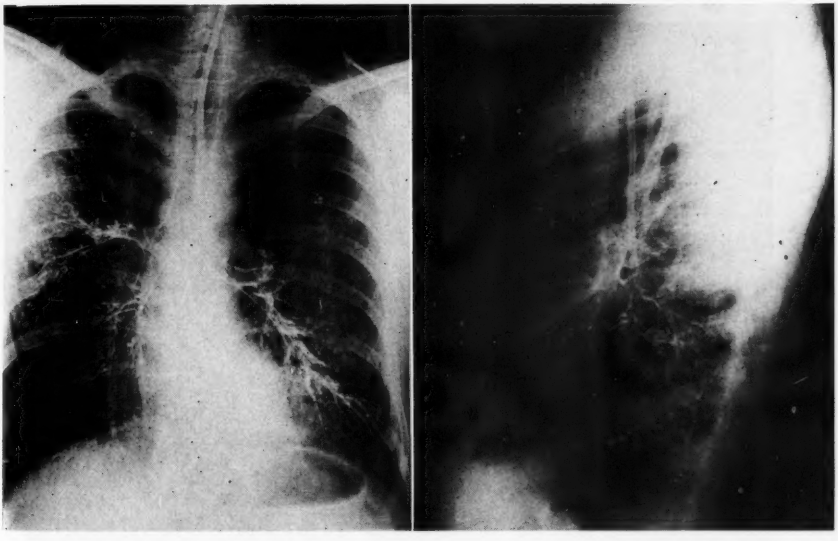
CASE 5.—R. H., a 4-year-old white boy, had had repeated episodes of left lower lobe pneumonia during the previous year. Roentgenograms showed a left lower lobe shadow consistent with unresolved pneumonia (Fig. 3, *A* and *B*). An excision of the basilar segments was performed. They showed bronchiectasis with numerous abscesses. The anomalous vessel to these segments arose from the lower thoracic aorta.

CASE 6.—D. E. died on the first day of life from aspiration of vomitus. Besides congenital megacolon and bilateral partial ureteral obstruction, an extralobar sequestration or accessory lobe of the lung was found (Fig. 4).

CASE 7.—L. W., an 18-year-old white man, had had left lower lobe pneumonia 6 months previously with persistent radiographic changes. Roentgenograms showed segmental atelectasis of the left lower lobe and bronchograms showed some clumping of the bronchi in this area.

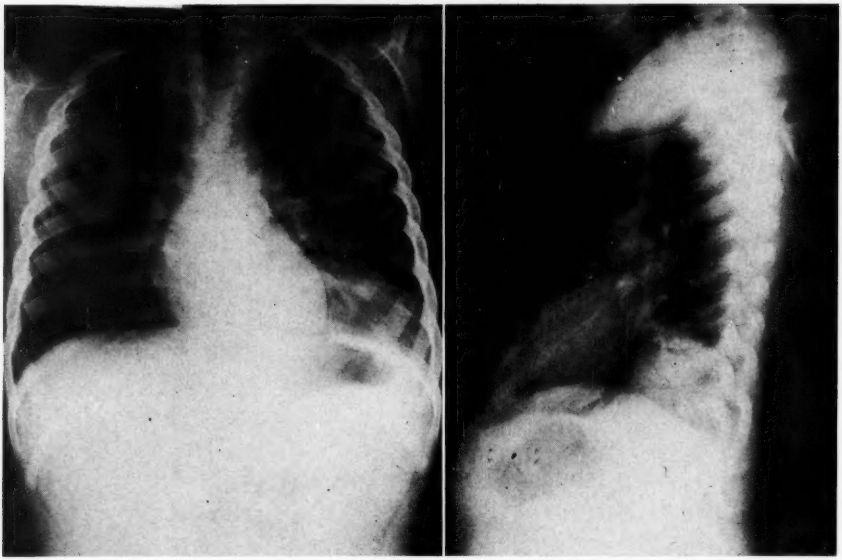


A.



B. *C.*

Fig. 2.—(Case 2.) *A* and *B*, Roentgenogram of the chest *(A)* and bronchograms *(B, C)* demonstrating the mass in the left lower lung field and the minimal amount of bronchiectasis in the lung tissue adjacent to it.



A. *B.*

Fig. 3.—(Case 5.) *A* and *B*, Chest roentgenograms showing the infiltrate in the posterior basilar area of the left lower lobe.

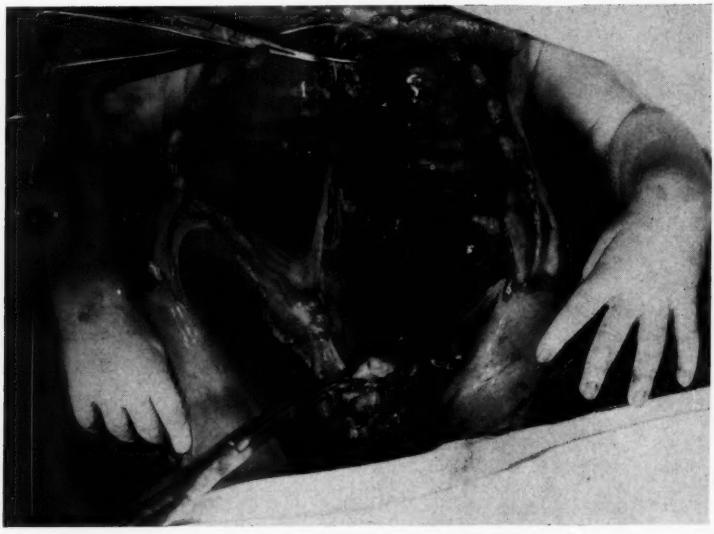


Fig. 4.—(Case 6.) Postmortem appearance of the extralobar pulmonary sequestration. Note the atelectatic accessory lobe and the vascular supply derived from the aorta. No bronchial communication could be demonstrated.

Bronchoscopy revealed bronchitis on the left, especially marked around the posterior basilar segment. At surgery a mass in the posterior basilar segment, receiving its blood supply directly from the aorta, was found. The basilar segments were resected. This area of chronic pneumonitis was supplied by both aortic and pulmonary branches but showed no bronchial communication.

DISCUSSION

Bronchopulmonary sequestration of the intralobar or extralobar types is usually a symptomatic lesion, but even when secondary infection or adjacent bronchiectasis does not call the patient's attention to the disease, a routine chest film probably will. These facts as well as the medical profession's increasing awareness of surgical pulmonary diseases mean that larger numbers of these lesions will be seen by surgeons than have been in the past. The surgeon treating these patients must be aware of the diagnostic possibility of bronchopulmonary sequestration whenever he sees a cystic or bronchiectatic lower lobe lesion, especially on the left side. The value of suspecting or recognizing this anomaly lies largely in minimizing the danger of accidental injury to the anomalous vessel during the pulmonary surgery.

SUMMARY

Seven cases of bronchopulmonary sequestration seen in the past 5 years have been described. All of these were on the left side and in male patients. The outstanding features of the disease in regard to clinical and pathologic findings and etiologic theories have been briefly reviewed.

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DUODENOBRONCHIAL FISTULA

With a Summary of Abdominothoracic Fistulas

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FISTULOUS CONNECTIONS between viscera are usually the result of ulceration, either benign or neoplastic, or secondary to gall stones. Such communications are usually between adjacent viscera. However, dissection and burrowing of an infectious, inflammatory, or ulcerative process may lead to the formation of a fistulous tract between widely separated structures either in the same body cavity or in adjacent ones. We wish to present a patient who had a duodenobronchial fistula. Despite a thorough search of the literature we have not encountered a report of a similar fistulous communication.

CASE REPORT

K. P., a 67-year-old man, was admitted to the West Side Veterans' Administration Hospital on June 27, 1955, because of a productive cough, weakness, and weight loss of 8 weeks' duration. His past history included a ruptured appendix in 1920 which was treated by drainage. Appendectomy was performed in 1922. One year later he had an episode of intestinal obstruction due to adhesions for which he was treated surgically. Another episode of intestinal obstruction occurred 6 years later, in 1929. In 1942, he underwent a cholecystostomy, but the details of his illness prior to this operation are unavailable. In 1950, he had been treated for pneumonitis at which time transitory hemoptysis was present.

During the month prior to his admission to the West Side Veterans' Hospital he had been hospitalized elsewhere, and a diagnosis of bronchiectasis had been made on the basis of x-ray and bronchoscopic findings. No evidence of tuberculosis or tumor had been demonstrated.

Physical examination disclosed an asthenic Negro man who appeared to be comfortable. The blood pressure was 118/70 mm. Hg. The heart was normal; there was a lag in respiratory movements of the chest. Resonance and breath sounds were decreased, and moist râles were scattered throughout the base of the right lung. There were three well-healed abdominal incisions resulting from his previous operations. The abdomen was otherwise normal as was the remainder of the physical examination.

The laboratory studies disclosed normal hemogram, serology, urinalysis, and electrocardiogram. Smears of gastric washings were negative for acid-fast bacilli on four occasions. The culture of the sputum revealed beta streptococcus and para-colon bacillus.

An x-ray study of the chest revealed diffuse mottling of the base of the right lung with slightly increased markings throughout the right lung field. There was displacement of the trachea and the heart to the right and some elevation of the diaphragm on the right (Fig. 1). These findings were considered compatible with the clinical diagnosis of bronchiectasis.

Bronchoscopy was negative except for the presence of purulent secretions in the segmental bronchi of the right lower lobe. The patient was treated for a time with

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Achromycin, Chlormycetin, and erythromycin with little benefit and without decrease in sputum. Following the studies thought pertinent to the productive cough, a more general investigation was begun.

Fluoroscopy following a barium meal disclosed a normal stomach and duodenal bulb. The junction of the first and second portions of the duodenum appeared to be retracted upward, laterally and posteriorly. From this point, barium escaped from the duodenal lumen into what was at first thought to be the common bile duct and its tributaries.

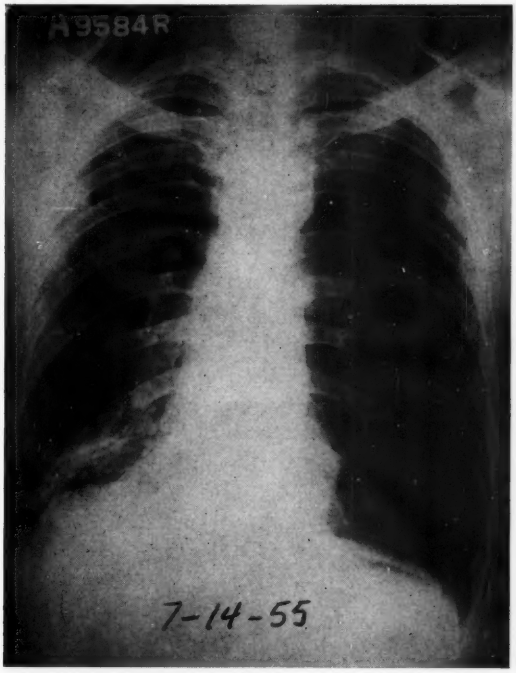

Fig. 1.—Roentgenogram which shows diffuse mottling of the base of the right lung, some shift of the mediastinum to the right, and elevation of the diaphragm on the right. These findings were considered compatible with the clinical diagnosis of bronchiectasis.

However, films made following the fluoroscopy showed that the barium had entered the bronchial radicles in the right lower lobe. Roentgen-ray studies in different projections demonstrated that a fistulous tract extended from the duodenum, passed posterior to the liver, traversed the diaphragm and entered the bronchial radicles of the posterior basal segment (Fig. 2). The second portion of the duodenum appeared to be smoothly compressed from the lateral side by an extrinsic mass. Intravenous cholecystography disclosed a distended gall bladder which was thought to account for the duodenal compression (Fig. 3).

Attempts to pass a long tube beyond the fistulous tract and the distorted duodenum for feeding purposes and to decrease the contamination of the tracheobronchial tree were unsuccessful. It was thought that closure of the fistula would decrease the productive cough.

On Aug. 8, 1955, the abdomen was opened through a right subcostal incision and the fundus of the gall bladder was found to be firmly attached to the abdominal wall, presumably at the site of the previous cholecystostomy. There were dense adhesions between the gall bladder and the duodenum. The duodenum, a short distance from the pylorus,

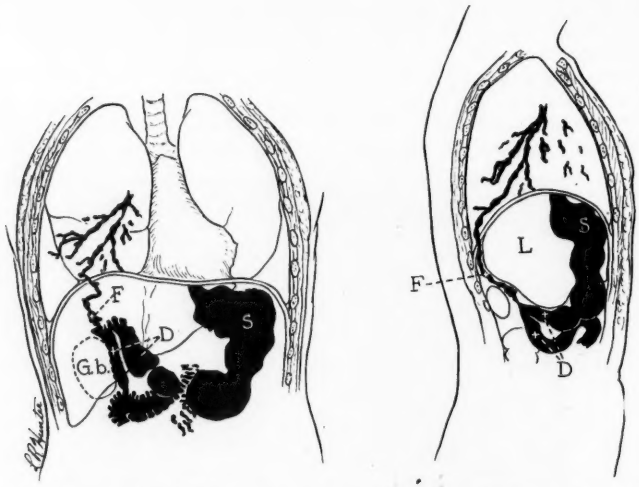

Fig. 2.—Tracings made from x-ray studies following a barium meal. The fistulous tract extended from the duodenum, passed posterior to the liver, traversed the diaphragm, and entered the bronchial radicles of the posterior segment of the lower lobe of the right lung.

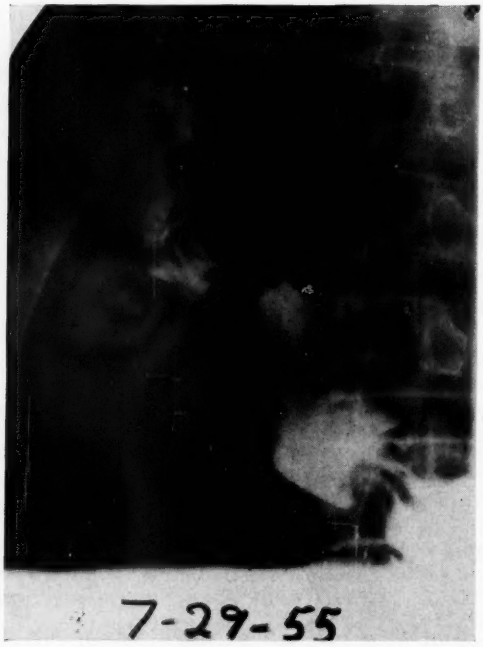

Fig. 3.—Intravenous cholecystography showed the compression of the third portion of the duodenum to be due to a distended gall bladder.

was seen to pass posteriorly and superiorly to the region of the posterior subphrenic space. It then made a sharp angulation at its point of contact with the lower edge of the posterior surface of the liver. The second portion of the duodenum was identified passing in its usual direction. The foramen of Winslow was patent.

The junction between the first and second portions of the duodenum was separated from the undersurface of the liver and from a mass of scar tissue involving the posterior edge of the liver and the diaphragm. The duodenum had an opening 1 cm. in diameter on its free border. An opening of similar size was found in the mass of scar tissue.

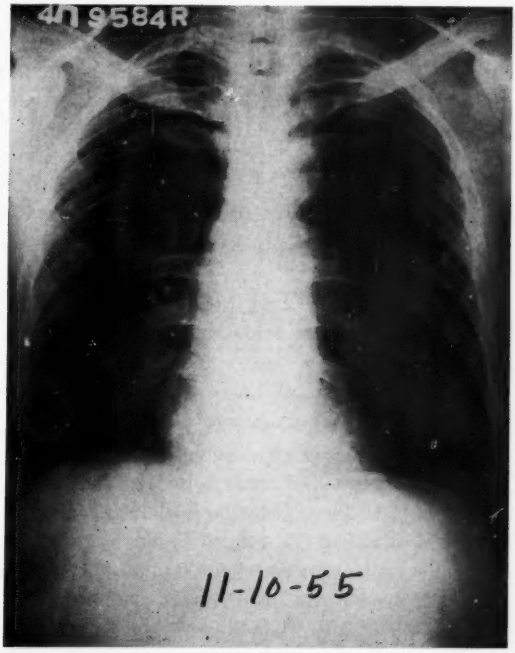

Fig. 4.—Roentgenogram of the chest made approximately 3 months after operation shows clearing of the lower lung field on the right, normal contour and level of the right diaphragm, and correction of mediastinal shift.

The duodenum revealed no other abnormality and no scarring, suggesting a chronic ulcer. The opening in the duodenum was closed with an inner row of catgut sutures and seromuscular sutures of cotton. The duodenum was displaced downward and wrapped in omentum to prevent the re-establishment of the fistula. A biopsy of the fistulous tract was taken. The gall bladder was removed. It was scarred and contained two stones, 1 cm. and 1.5 cm. in diameters. Suitable drains were put in place and the abdomen was closed.

The pathologic diagnosis was chronic cholecystitis and cholelithiasis and a fistulous tract with intestinal mucosa not further identified at the abdominal end. The early postoperative course was marked by episodes of chills and fever, and a white blood cell count of 48,000. By the fifth postoperative day, the temperature was normal and the white blood cell count was 14,000. The abdomen was soft, the Levine tube was removed and the patient received a liquid diet. A bronchogram on Aug. 26, 1955, failed to show any evidence of bronchiectasis of the middle or right lower lobes. A postoperative gastrointestinal study revealed less distortion of duodenum. Comparison of the preoperative and postoperative chest films showed considerable clearing in the right lower lung field (Fig. 4).

Following operation, the patient recovered rapidly. His cough subsided. He was dismissed from the hospital on Dec. 14, 1955, having been detained for completion of extensive dental care.

DISCUSSION

In the search for a previously recorded instance of duodenobronchial fistula, a variety of pathologic conditions below the diaphragm, which eventually communicated with the bronchial tree, were encountered. A summary of these widely scattered reports is offered.

It has, of course, been well established that subphrenic suppurative processes of long standing can eventually penetrate the diaphragm to cause empyema, pericarditis, pleurisy with effusion, or bronchial fistula. In the collective review of 3,608 patients with subphrenic abscesses, compiled by Ochsner and De Bakey,[1] 28.1 per cent had pleurisy or pleural effusion, 17.8 per cent had empyema, and 10.5 per cent had bronchopleural fistulas.

Hochberg's[2] series of 111 patients had a similar high incidence of these complications with 36 per cent, 19.2 per cent, and 4.7 per cent of pleurisy or pleurisy with effusion, empyema, and bronchopleural fistulas, respectively. Berens, Gray, and Dockerty[3] in reporting subphrenic abscesses in 154 patients, found pleural effusion in 54.5 per cent, empyema in 22.7 per cent, and bronchopleural fistulas in 11 per cent. The occurrence of bronchopleural fistula complicating subphrenic abscess appears to be well established.

Gullickson and Smith[4] have emphasized the desirability of immediate treatment for patients with subphrenic abscesses, who develop "bronchopleural-peritoneal" fistulas. They describe in detail 2 patients in whom rapid deterioration occurred following the establishment of this type of fistula and in whom bronchoscopic aspiration in one patient and tracheostomy and aspiration in the other appeared to be lifesaving.

Adams,[5] in discussing pleurobiliary and bronchobiliary fistulas, points out that most of these are associated with abdominothoracic war wounds and warns that if bile is found at thoracentesis, prompt drainage of the pleural space should be established. It is also urgent, he states, to establish adequate drainage in patients who cough up bile, as a fatal necrosing bronchitis may result from the action of bile plus secondary infection.

Adams reported 4 patients, 2 of whom developed empyema thoracis after rupture of a gangrenous gall bladder. Open drainage of the empyema cavity was done in both patients. Bile drained until appropriate biliary surgery was performed, after which the empyema healed. In the other 2 patients, a bronchobiliary fistula developed after cholecystectomy which was followed by jaundice. The eradication of common duct strictures in both of these patients was followed by the healing of the bronchobiliary fistulas.

Meyer,[6] in reporting the rupture of a pyogenic subphrenic abscess into the pericardium, emphasized the rarity of this occurrence. He also states that rupture of amebic liver abscess into the pericardium is rare, as it requires an abscess of the left lobe of the liver, an uncommon location. Gastric ulcers

have ruptured into the pericardium. The use of antibiotics masks the symptoms of the original disease in many instances and may be responsible for delayed or missed diagnoses.

Neilsen, Dick, and Maddock (1950),[7] in reporting a perinephrobronchial fistula and psoas abscess with chronic perinephric infection, emphasize the insidious nature of perinephric infection and the great frequency of its late diagnosis. Their patient coughed up as much as two quarts of pus per day. Diagnoses of bronchiectasis and of carcinoma of the lung had previously been made. A mass developed in the right groin. Expectoration of large amounts of pus made the mass smaller. The cough stopped after the mass was drained of two quarts of pus. A urethral catheter was kept in the sinus in the right groin for 3 years. Healing occurred when it was removed.

Ribeiro (1939)[8] describes a patient who for 3 months had expectorated large quantities of foul sputum. Incision into a swelling in the left flank yielded 3 L. of pus. The foul expectoration persisted, as did a fistula in the incision. Roentgenograms showed a voluminous calculus in the region of the left kidney. At the second operation it was removed in pieces and a nephrectomy was done. As the upper pole of the kidney was being freed from the diaphragm, a "lumbobronchial" fistula was found. The patient was under spinal anesthesia and began to cough bloody mucopurulent material. Cough and expectoration stopped 8 days later. The fistula in the flank persisted and opaque media injected into it entered what appeared to be small bowel, as judged by the mucosal pattern. Curetting and packing the fistula was followed by healing. It is possible that a loop of small bowel had become adherent to the infected kidney and that the fistula occurred at this point.

Urizza and Gama,[9] in 1954, reported a patient with hemoptysis and, later, mucopurulent sputum. Following a barium meal, he expectorated barium, and a diagnosis of gastrobronchial fistula was made. His complete preoperative diagnosis was diaphragmatic hernia, gastrobronchial fistula, and bronchiectasis of the left lower lobe or lingula. At operation an "anterior" diaphragmatic hernia was found. A fistula had developed between the intrathoracic portion of the stomach and the tip of the lingula. A partial gastric resection was done to remove the area of the fistulous opening. The hernia was repaired, and a lingulectomy was performed. Microscopic examination of the lingula disclosed atelectasis, fibrosis, cystic bronchiectasis, nonspecific bronchial infection, and lipoid pneumonia. The patient made a prompt recovery and was ambulatory after the fourth postoperative day.

We are unable to prove the sequence of events which led to the formation of the fistula in our patient. He was well for 6 years after drainage of the gall bladder; therefore, injury to the duodenum during the operation is not considered responsible. Then an episode of "pneumonitis with hemoptysis" occurred. However, it was not until 5 years later that bronchiectasis was diagnosed. At the operation for the bronchoduodenal fistula there appeared to be no findings suggesting serious gall bladder disease, such as gangrene or continuing fibrosis. There was no evidence of malignant disease.

We are left with two reasonable possibilities. One is the perforation of a duodenal diverticulum. This appears to be rather unlikely as they are usually

on the pancreatic side of the duodenum. On a percentage basis, perforation of duodenal diverticulitis seems unlikely as Byerly,[10] writing in 1948, found only 5 previously reported cases, all, by the way, on the "concave" side of the second portion of the duodenum.

The other possibility is the perforation of a duodenal ulcer at the junction of the second and third portions of the duodenum with sufficient walling-off to prevent a subphrenic abscess but not enough to prevent a burrowing behind the liver, through the diaphragm, and into a basilar bronchus. Duodenal ulcers are found in the first 5 cm. of the duodenum, as a general rule, and not commonly in other portions; however, they have been found in all parts of the duodenum. From the above considerations we believe that the primary disease leading to this unusual fistula was a perforated duodenal ulcer.

SUMMARY

The occurrence of a duodenobronchial fistula in a 67-year-old man is reported. His chief complaint was productive cough and a diagnosis of bronchiectasis of the right lower lobe had been made. Roentgenograms of the gastrointestinal tract showed that barium left the duodenal lumen and reached the bronchial radicles of the lower lobe of the right lung through a fistulous communication.

At operation, the duodenum was separated from the fistulous tract and the opening in the duodenum was closed. The gall bladder which contained two stones and did not appear to be involved in the fistula formation in any way was removed as an incidental procedure. The productive cough stopped following the operation and the x-ray studies showed clearing of the haziness in the right lower lobe. From a consideration of the course and findings in this patient, a perforated duodenal ulcer appears to be the most likely original lesion.

A summary of abdominothoracic fistulas is presented.

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COCCIDIOIDOMA

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COCCIDIOIDOMA is a lesion which is endemic to the southwestern part of the United States. Thus, in most collective series of pulmonary granulomas, the fungus *Coccidioides immitis* is rarely isolated as the causative agent. The lack of familiarity with this lesion has led many clinicians to picture the coccidioidoma as a solid granuloma without a virulent potential. That such lesions are not generally solid nor sterile is well borne out by the following presentation of patients. The chest x-ray studies and gross pathologic findings are illustrated by the accompanying photographs of a typical case (Figs. 1 and 2).

MATERIALS AND METHODS

During the 10-year period from 1948 to 1958, 25 cases of coccidioidoma were treated surgically on the County and private thoracic surgical services in Bakersfield, California. On initial x-ray examination these cases met the following criteria: (1) location in the substance of the lung, (2) no apparent cavitation, (3) absence of obstructive changes in the lung peripheral to the lesion, and (4) no other significant pathological change in the lung fields. The causative organism was observed in every case, on the wet mount preparation, in the stained sections, or by culture.

OBSERVATIONS

There were 22 Caucasians, 2 Negroes, and 1 Filipino involved in this series. The lesion was found in 13 males and 12 females with the age range evenly distributed between 20 and 60 years of age for both sexes (Table I).

TABLE I. AGE AND SEX

	AGE (YEARS)							
	-20	21-30	31-40	41-50	51-60	61-70	71-80	TOTAL
Male	1	2	2	3	3	1	1	13
Female		3	4	2	2	1		12
Totals	1	5	6	5	5	2	1	25

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No acute or pneumonic history was elicited in 12 patients, the lesion being detected on a survey chest roentgenogram (Table II). In those 13 patients presenting symptoms, the interval between x-ray findings and surgery was less than 3 months in 5 patients and over 12 months in 8. The latter group illustrates the tendency to observe these lesions for extended periods of time in certain cases.

TABLE II. CLINICAL HISTORY

	INTERVAL BETWEEN X-RAY FINDING AND SURGERY	
	UNDER 3 MO.	12 MO. AND OVER
Symptoms prompting x-ray	5	8
Asymptomatic: routine film	12	

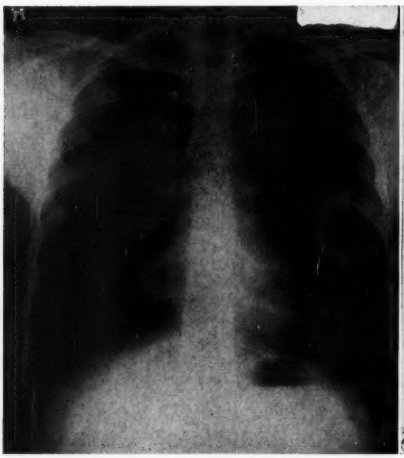

Fig. 1.

Fig. 2.

Fig. 1.—Posteroanterior roentgenogram of the chest in a 21-year-old man. Note the coccidioidoma in the right upper lobe.

Fig. 2.—Photograph of gross specimen disclosed in Fig. 1.

Skin tests for coccidioidomycosis were done presurgically on 18 patients, and in 11 of them the reaction was positive. Positive tuberculin reactions were obtained in 6 of 15 patients tested. Five symptomatic patients exhibited negative coccidioidin skin tests at the time of surgery. Retesting a number of weeks later might have shown a conversion to a positive reaction, but the possibility of malignancy precluded such a waiting period in some cases. Positive precipitin and complement fixation titers were obtained in 2 and 4 cases, respectively, out of 16 cases tested (Table III).

TABLE III. SEROLOGY

	16 CASES TESTED	
	POSITIVE	NO REACTION
Precipitin titer	2	14
Complement fixation	4	12

The indications for surgery fall into two principal groups: (1) a round lesion in which the possibility of malignancy cannot be ruled out, and (2) a radiodensity which intermittently cavitates.

The peripheral location of the coccidioidoma makes bronchoscopy, node biopsies, and cytologic studies of the sputum unrewarding in making a diagnosis as in other peripherally located tumors. The intermittently cavitating granuloma must be considered as a possible source of seeding of other areas of the pulmonary parenchyma. That such contamination does take place is suggested by 1 case in this series.

Preoperative chest x-ray studies were inconclusive in ascertaining the etiology of the solitary lesion until, as occurred in 6 cases, the onset of radiolucency or air-fluid levels. In the remaining 19 cases, the absence of calcium made carcinoma at least suspect in every case. However, microscopic examination of the surgical specimen did reveal scattered central calcification in 4 cases. The significant finding of lamination which is considered pathognomonic for granulomas was not observed in roentgenograms and fibrous lamination was seen grossly in only 2 cases.

The anatomic location of the coccidioidoma showed equal distribution between the upper and lower lobes, the right lower lobe and the left upper lobe containing 15 of the 25 lesions. Previous work emphasized the tendency for occurrence near the lower and mid-lung fields. It would seem there is no actual lobe preference.

The gross size of the granulomas varied from 1.2 cm. to 4 cm., with the average diameter of all lesions being 2.4 cm. (Table IV).

TABLE IV. GROSS SIZE OF LESION

	SIZE (CENTIMETERS)*						
	UNDER 1 CM.	1.0-1.5	1.6-2.0	2.1-2.5	2.6-3.0	3.1-3.5	3.6-4.0
Number of cases	0	2	8	5	5	3	2

*X-ray measurement larger.

The gross pathology was uniform. All of the coccidioidomas exhibited a fibrous capsule varying from 1 to 4 mm. in width, and in all there was central necrosis or caseation (Table V). As mentioned previously, two nodules contained fibrous lamination.

TABLE V. GROSS PATHOLOGY

Fibrous capsule	25 cases
Central necrosis	25 cases
Solid granuloma	0 cases
Lamination present	2 cases

The difficulty of obtaining a specific diagnosis in a granulomatous lesion is well known to the thoracic surgeon. The methods used in this series are tabulated in Table VI. The occasional discovery of coccidioidal spherules in the

wet mount, when all other methods are negative, illustrates the problem of causative organism identification. Also of interest is the 1 case of a positive culture on material taken from the surgical specimen, yet the wet mount and stained sections failed to disclose the organism. Unless all available means of organism detection are utilized, the diagnosis of nonspecific granuloma will be a common one.

TABLE VI. DETECTION OF COCCIDIOIDAL ORGANISM IN ALL 25 CASES

Wet mount preparation	14	Positive Coccidioides culture on sputum	1
Permanent surg. section:		Culture on surgical specimen	2
A. Spherules	19	Positive wet mount with negative microscopic	2
B. Mycelia	4	Negative wet mount, negative microscopic with positive culture	1
Spherules in sputum	1		

In 3 patients, postoperative difficulties occurred. Two of the problems were atelectasis and both were cleared by bronchoscopy. The third complication was venous thrombosis of the lower extremities.

EXTENT OF RESECTION

Surgery performed here for coccidioidoma is usually of a segmental or subsegmental nature, as is implied by their location and average diameter of approximately 2.5 cm. (Table VII). On occasion, a lobe or more must be resected because of chronic inflammation or a hilar position. The extent of resection in coccidioidal granuloma and cavitation has been much discussed in regard to recurrent disease and postoperative complications. Satellite nodules have been held responsible for postoperative empyema and pulmonary dissemination of the fungus or recurrent cavitation. Some thoracic surgeons thus perform lobectomy as the minimal procedure. In our series, partial lobectomy was done in 17 out of 25 cases, and in none of these did postoperative difficulties occur which were related to the organism. In the 1 case requiring pneumonectomy, the lesion initially presented as a solid granuloma and then progressed to the stage of multiple cavities. A lesser procedure was not feasible at the time of surgery since a large cavity involved almost the entire left upper lobe and a smaller cavity was intimately adherent to the vascular supply to the lower lobe.

TABLE VII. EXTENT OF PULMONARY RESECTION

Subsegmental lobectomy (wedge)	13 cases
Segmental lobectomy	4 cases
Lobectomy	7 cases
Pneumonectomy	1 case

DISCUSSION

There is general agreement that an undiagnosed solitary pulmonary nodule deserves excision, and a large number of coccidioidomas are removed for suspected malignancy. Most reports of so-called coin lesions list malignancy as the

etiology in some 20 to 35 per cent of cases. In an endemic area, such as the San Joaquin Valley of California, malignancy is found in a much smaller percentage. The coccidioidin skin test is not an effective differential tool, since most residents of this area have a positive reaction. Likewise, the coccidioidal serologic findings are of little value, since in most cases of chronic granuloma the host immune response has resolved to levels that cannot be detected.

In those cases in which coccidioidomycosis is the presumptive preoperative diagnosis, the surgical indications largely relate to persistent cavitation and its accompanying symptoms. Some physicians regard both coccidioidal cavitation and coccidioidomas as asymptomatic lesions rarely requiring surgery. While it is undoubtedly true that there are many undiagnosed asymptomatic granulomas, it is of interest that 13 of the 25 patients in this series were seen because of persistent respiratory symptoms.

The epidemiology of the coccidioidoma is important in evaluating the surgical indications for its removal. That viable organisms are present in the granuloma wall in both spherule and/or mycelia form is a fact, yet man to man transmission of the disease or later extrapulmonary dissemination from a pulmonary focus has never been proved. More likely is the possibility of endobronchial spread of the fungus as a process of shelling occurs. In such a situation the inoculating dose could be large enough to set up a new site of pulmonary disease in spite of the patient's immune response. Cavitation at secondary sites in the presence of granuloma has been reported by others and was found in 1 case in this series. Another explanation of the later appearance of cavitation could be that undetected foci of fungal infection were present in the lung and became detectable with renewed activity. In any case, they attest to the spreading potentialities of the organism in nondisseminated cases of pulmonary lesions.

SUMMARY

Twenty-five cases of coccidioidoma are presented, in all of which the fungus has been recovered in the surgical specimen. Twelve of the patients were asymptomatic, while 13 initially presented symptoms. The principal surgical indications were the possibility of malignancy and recurrent cavitation. Skin tests, coccidioidal serology, and chest x-ray studies were of limited positive value in making a specific diagnosis. The gross pathologic findings are stressed, there being central necrosis with a fibrous capsule in all lesions. Surgery consisted of partial lobectomy in most cases, and there has been no apparent spread or recurrent disease in these cases.

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THE AMERICAN ASSOCIATION FOR THORACIC SURGERY

FORTIETH ANNUAL MEETING

MAY 11, 12, AND 13, 1960

DEAUVILLE HOTEL, MIAMI BEACH, FLA.

Program

MEMORANDA FOR GUIDANCE OF SPEAKERS

1. In accordance with the By-Laws of the Association, the papers which are read at the meeting shall be given to the Reporter *immediately after presentation.* If these papers are not submitted promptly their publication may be delayed.
2. In publication it is customary to group discussions together on a series of papers. Any delay in the return of corrected discussions to the Editor means that publication of all papers on the subject will be held up. This is manifestly unfair to those who are conscientious in the prompt submission of their remarks for publication. Undue tardiness may mean that the discussion will not be published.
3. *Regular Program:* Speakers will be limited to 15 minutes.
4. *Thoracic Surgery Forum:* Speakers will be limited to 10 minutes. Papers on the Thoracic Surgery forum as submitted for publication will be limited to 3,000 words. At the discretion of the President, limited discussion will be allowed following the formal presentations.
5. *Discussion of Papers:* Discussers will be limited to 3 minutes. Only members of the Association and invited speakers will have the privilege of discussing papers.

Wednesday Morning, May 11, 1960

8:30 A.M. Business Meeting (Limited to Members)
Napoleon Room

8:45 A.M. Scientific Session: REGULAR PROGRAM
Napoleon Room

1. **The Use of Direct Myocardial Stimulating Electrodes in Complete Atrioventricular Block.** Bernard S. Levowitz (by invitation), William B. Ford, and James W. Smith, Jr. (by invitation), Pittsburgh, Pa.
2. **Surgical Correction of Transposition of the Great Vessels. A Five-Year Survey.** Thomas G. Baffes, Maurice Lev (by invitation), Milton H. Paul (by invitation), Robert A. Miller (by invitation), William L. Riker (by invitation), Arthur DeBoer (by invitation), and Willis J. Potts, Chicago, Ill.
3. **Surgical Palliation in Patients With Ebstein's Anomaly and Congenital Hypoplasia of the Right Ventricle.** Milton Weinberg, Jr. (by invitation), Juan P. Bicoff (by invitation), Lawrence Luan (by invitation), Zwi Steiger (by invitation), Benjamin M. Gasul (by invitation), and Egbert H. Fell, Chicago, Ill.
4. **Myocardial Infarction in Infancy: The Surgical Management of a Complication of Congenital Origin of the Left Coronary Artery From the Pulmonary Artery.** David C. Sabiston, Jr., Salvatore Pelargonio (by invitation), and Helen B. Taussig (by invitation), Baltimore, Md.

5. **Diagnosis and Surgical Treatment of Intracardiac Myxoma and Rhabdomyoma.** Rodman E. Taber and Conrad R. Lam, Detroit, Mich.
6. **Vasomotor Activity During Total Body Perfusion.** Paul W. Sanger, Frederick H. Taylor, and Francis Robicsek (by invitation), Charlotte, N. C.

Wednesday Afternoon, May 11, 1960

2:00 P.M. Scientific Session: REGULAR PROGRAM
Napoleon Room

7. **Studies of Peripheral Vascular Resistance Associated With Total Cardiopulmonary Bypass. I. Peripheral Resistance Under Condition of Normothermia and Normotension.** A. Robert Cordell (by invitation), Merrill P. Spencer (by invitation), and Jesse H. Meredith (by invitation), Winston-Salem, N. C.
8. **Lipuria and Lipasemia After Thoracic Surgical Procedures.** F. Price Cossman (by invitation), Federico Adler (by invitation), and C. Frederick Kittle, Kansas City, Kans.
9. **Analysis of Fifty Cases of Pulmonary Emphysema, Blebs, and Bullae Treated Surgically.** Jerome R. Head, Theodore R. Hudson, Louis R. Head (by invitation), and James M. Head (by invitation), Chicago, Ill.
10. **Lung Abscess in Japan.** Kingo Shinoi (by invitation), Tokyo, Japan.
11. **A Study of Essential Hemoptysis.** Raymond J. Barrett and William M. Tuttle, Detroit, Mich.
12. **Ligation and Division of the Bronchus in the Surgical Treatment of Cavitary Tuberculosis.** J. Maxwell Chamberlain and Thomas M. McNeill (by invitation), New York, N. Y.
13. **The Culture of Tubercle Bacilli from Resected Specimens of "So-called" Negative Patients.** William P. Coghlan (by invitation), George S. Willauer, Charles Fineberg (by invitation), and Robert G. Johnson (by invitation), Philadelphia, Pa.

Thursday Morning, May 12, 1960

8:30 A.M. Scientific Session: THORACIC SURGERY FORUM
Napoleon Room

14. **The Subcoronary Implantation of a Flexible Tricuspid Aortic Valve Prosthesis.** Benson B. Roe, Mervyn F. Burke (by invitation), and Harry Zehner (by invitation), San Francisco, Calif.
15. **Experimental Production of Aortic Stenosis.** Anthony J. Munoz (by invitation), and Sam E. Stephenson, Jr. (by invitation), Nashville, Tenn.
16. **Evaluation of a New Nonwettable Macroporous Membrane With High Permeability Constants for Possible Use in a Membrane Oxygenator.** James S. McCaughan (by invitation), Richard Weeder (by invitation), John C. Schuder (by invitation), and William S. Blakemore, Philadelphia, Pa.
17. **Temperature Compensated, Self-Calibrated Oxygen Monitoring Device.** Jesse H. Meredith (by invitation), John H. Artesani (by invitation), and Joseph Mamlin (by invitation), Winston-Salem, N. C.
18. **Pulmonary Arterial Hypoxia Versus Inspiratory Hypoxia in Relation to Increased Pulmonary Vascular Resistance.** Peter V. Moulder, Joseph Lancaster (by invitation), Robert W. Harrison (by invitation), Stephen Michel (by invitation), and Richard G. Thompson (by invitation), Chicago, Ill.
19. **Treatment of Bank Blood by Resins.** Edward D. McLaughlin (by invitation), Thomas F. Nealon, Jr., and John H. Gibbon, Jr., Philadelphia, Pa.

20. **Gas-Exchange Dynamics of Glycerolized Frozen Blood.** Thomas G. O'Brien (by invitation), Chelsea, Mass., and Elton Watkins, Jr., Boston, Mass.
21. **The Relationship of the Sympatho-Adrenal System to Potassium Flux and Cardiac Irritability Induced by Alterations in Blood pH.** Bernard Goott (by invitation), J. Rosenberg (by invitation), R. C. Lillehei (by invitation), Fletcher A. Miller (by invitation), and Owen H. Wangensteen, Minneapolis, Minn.
22. **Bronchoscopy and Bacteremia.** Sheldon Oscar Burman (by invitation), Pittsburgh, Pa.
23. **Altered Hemodynamics in the Pulmonary Circulation Following Reaeration of an Atelectatic Lung.** Edwin Tutt Long (by invitation), Arthur F. Reimann (by invitation), Takamaru Mikouchi (by invitation), John R. Benfield (by invitation), and Salvatore L. Nigro (by invitation), Chicago, Ill.
24. **Selective Chemotherapy of the Lung During Unilateral Pulmonary Arterial Occlusion With a Balloon-Tipped Catheter.** Nicholas P. D. Smyth (by invitation), and Brian Blades, Washington, D. C.
25. **An Experimental Study of Pulmonary Artery Replacement.** Joseph W. Gilbert, Jr. (by invitation), William P. Cornell (by invitation), and Theodore Cooper (by invitation), Bethesda, Md.
26. **A Simple Device for the Mechanical Anastomosis of Blood Vessels.** Timothy Takaro, Oteen, N. C.
27. **Experimental Left Coronary Artery Perfusion Through an Aortotomy During Cardiopulmonary Bypass.** James B. Littlefield (by invitation), Edward M. Lowicki (by invitation), and William H. Muller, Jr., Charlottesville, Va.
28. **Growth of Cardiovascular Chambers Following Cardiac and Aortic Surgery.** Sigmund A. Wesolowski (by invitation), Lester R. Sauvage (by invitation), Philip N. Sawyer (by invitation), and Karl E. Karlson, Brooklyn, N. Y.

Thursday Afternoon, May 12, 1960

2:00 P.M. Executive Session (Limited to Active and Senior Members)
Napoleon Room

3:00 P.M. Scientific Session: REGULAR PROGRAM
Napoleon Room

Address by the President, William E. Adams, Chicago, Ill.

Address by Honored Guest, Alfonso Topete, Chairman, Department of Surgery, University of Guadalajara, Mexico. **New Findings in the Coronary-Encephalic Perfusion in Depressive Surgical Cases.**

29. **Coarctation of the Aorta With Particular Emphasis Upon Improved Techniques of Surgical Repair.** George C. Morris, Jr. (by invitation), Denton A. Cooley, Michael E. De Bakey, and E. Stanley Crawford, Houston, Tex.

7:00 P.M. Banquet and Dancing, Casanova Room
Attendance limited to Members of the Association and their ladies, Invited Speakers and their ladies.
Dinner dress preferred.

Friday Morning, May 13, 1960

9:00 A.M. Scientific Session: REGULAR PROGRAM
Napoleon Room

30. **A Five-Year Follow-up Study of Closed Mitral Valvulotomy.** J. Gordon Scannell, John F. Burke (by invitation), and Farrokh Saidi (by invitation), Boston, Mass.

31. **Valvuloplasty for Acquired Aortic Stenosis.** Donald G. Mulder (by invitation), Albert A. Kattus (by invitation), and William P. Longmire, Jr., Los Angeles, Calif.
32. **Partial and Complete Aortic Valve Prostheses in Advanced Aortic Insufficiency.** Dwight E. Harken, Warren J. Taylor (by invitation), Harry S. Soroff (by invitation), Armand A. Lefemine (by invitation), Sushil K. Gupta (by invitation), and Steven Lunzer (by invitation), Boston, Mass.
33. **The Results of Surgical Treatment for Ventricular Septal Defect.** John W. Kirklin, Dwight C. McGoon, and James W. DuShane (by invitation), Rochester, Minn.
34. **The Closure of Atrial Septal Defects Utilizing General Hypothermia: The Effectiveness of Treatment as Determined by Cardiac Catheterization.** Andrew G. Morrow, Joseph W. Gilbert, Jr. (by invitation), R. Robinson Baker (by invitation), and N. Perryman Collins (by invitation), Bethesda, Md.
35. **Elective Cardiac Arrest Using Selective Cardiac Hypothermia.** David M. Long, Jr. (by invitation), Laurence P. Sterns (by invitation), Vincent L. Gott (by invitation), Robert H. DeRiemer (by invitation), and C. Walton Lillehei, Minneapolis, Minn.
36. **Open Heart Surgery Using Deep Hypothermia Without an Oxygenator.** Archer S. Gordon (by invitation), Bertrand W. Meyer, and John C. Jones, Los Angeles, Calif.

Friday Afternoon, May 13, 1960

2:00 P.M. Scientific Session: REGULAR PROGRAM
Napoleon Room

37. **Clinical Experiences With Fifteen Patients With Traumatic Rupture of the Thoracic Aorta.** Frank C. Spencer, Paul F. Guerin (by invitation), Hu A. Blake (by invitation), Washington, D. C., and Henry T. Bahnson, Baltimore, Md.
38. **Surgical Management of Penetrating Injuries of the Ascending Aorta and Aortic Arch.** Walter L. Diveley, Rollin A. Daniel, Jr., and H. William Scott, Jr., Nashville, Tenn.
39. **Antibiotics and Extracorporeal Surgery.** C. Frederick Kittle, and William A. Reed (by invitation), Kansas City, Kans.
40. **Achalasia of the Esophagus in Children.** Orvar Swenson, and Chris T. Oeconomopoulos (by invitation), Boston, Mass.
41. **Objective Evaluation of Surgery for Hiatus Hernia and Esophagitis.** Lucius D. Hill, and Kyle W. Chapman (by invitation), Seattle, Wash.
42. **Instrumental Perforation of the Esophagus.** Thomas F. Nealon, Jr., John Y. Templeton III, Vincent D. Cuddy (by invitation), and John H. Gibbon, Jr., Philadelphia, Pa.